Vaccine and Related Biological Products Advisory Committee

March 15, 2005

ADACEL™

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

sanofi pasteur

Adacel - Agenda

Introduction	**Luc Kuykens, MD, MPH** **VP Regulatory Affairs**
Pertussis Epidemiology	**David Johnson, MD, MPH** **Director Scientific and Medical Affairs**
Immunogenicity	**Michael Decker, MD, MPH** **VP Scientific and Medical Affairs**
Safety and Conclusion	**Luc Kuykens, MD, MPH** **VP Regulatory Affairs**

Public Health Need for Adolescent and Adult Pertussis Vaccination

- **Reduce morbidity associated with pertussis in all age groups**
- **Reduce pertussis disease in adolescents and adults**
- **Prevent transmission of pertussis from adolescents and adults to infants**

Vaccine Formulation

	Adacel	Daptacel	Td Adsorbed
Tetanus Toxoid	5 Lf	5 Lf	5 Lf
Diphtheria Toxoid	2 Lf	15 Lf	2 Lf
5 Component Pertussis Vaccines			
Pertussis Toxoid	2.5 μg	10 μg	-
Filamentous Hemagglutinin	5 μg	5 μg	-
Pertactin	3 μg	3 μg	-
Fimbriae Types 2 and 3	5 μg	5 μg	-

Adjuvant: 0.33 mg aluminum
0.6% v/v 2-phenoxyethanol

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Importance of FIM in the 5-Component Acellular Pertussis Vaccines

- **The importance of PRN and FIM in protection against typical pertussis was established in the household contact study nested in Sweden I Efficacy Trial[1]**
- **Efficacy correlated with having high titers of anti-PRN (75%), high anti-FIM (72%), or both (85%)**
- **Two other household contact studies also support an important role for FIM[2,3]**

[1]Storsaeter J, Hallander HO, Gustafsson L, et al. *Vaccine.* 1998;16:1907-1916;
[2]Cherry JD, Gornbein J, Heininger U, et al. *Vaccine.* 1998;16:1901-1906;
[3]Deen JL, Mink CM, Cherry JD, Christenson PD, Pineda EF, Lewis K, Blumberg DA, Ross LA. *Clin Infect Dis*. 1995;21(5):1211-9.

Adacel Components

- **All components of Adacel are licensed immunogens in Daptacel or Td adsorbed**
- **The manufacturing and testing methods for components of Adacel are the same as those used for Daptacel and Td adsorbed**
- **Manufactured in Daptacel production facility**

Adacel Clinical Development Program

- **Demonstration of non-inferiority for:**
  - **Safety**
    - **Comparison to standard of care (Td adsorbed vaccine)**
  - **Immunogenicity**
    - **Comparison to standard of care (Td adsorbed vaccine) for diphtheria and tetanus**
    - **Comparison to efficacious 5 component DTaP vaccine for pertussis**
- **Concomitant administration with hepatitis B (HB) or influenza vaccine**

Adacel Clinical Experience

Population	US Licensure Trials	Supportive Canadian Trials	Total
Adults	2448	638	3086
Adolescents	3393	324	3717
TOTAL	5841	962	6803

Post-marketing experience: > 6 million doses of Adacel-containing vaccines distributed.

Adacel Key Findings

- **Safe and well tolerated among adolescents and adults**
- **Similar safety profile as licensed Td vaccine**
- **Achieved all pre-specified non-inferiority criteria for immunogenicity vs. Td**
- **One dose in adolescents and adults produces pertussis antibody levels exceeding 3 doses of Daptacel**
- **Can be given concomitantly with HB vaccine or influenza vaccine**

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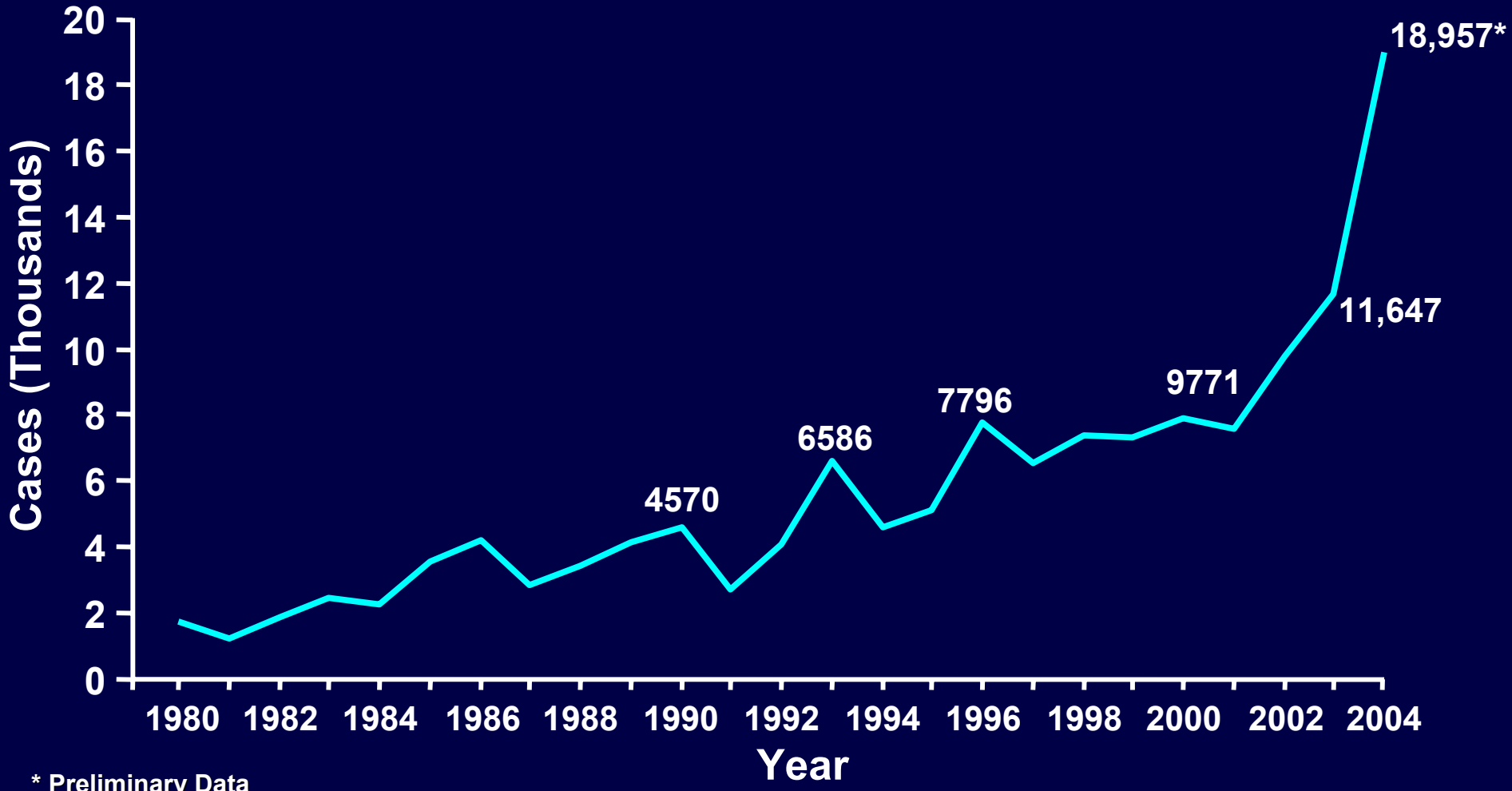
Safety and Conclusion	Luc Kuykens, MD, MPH VP Regulatory Affairs

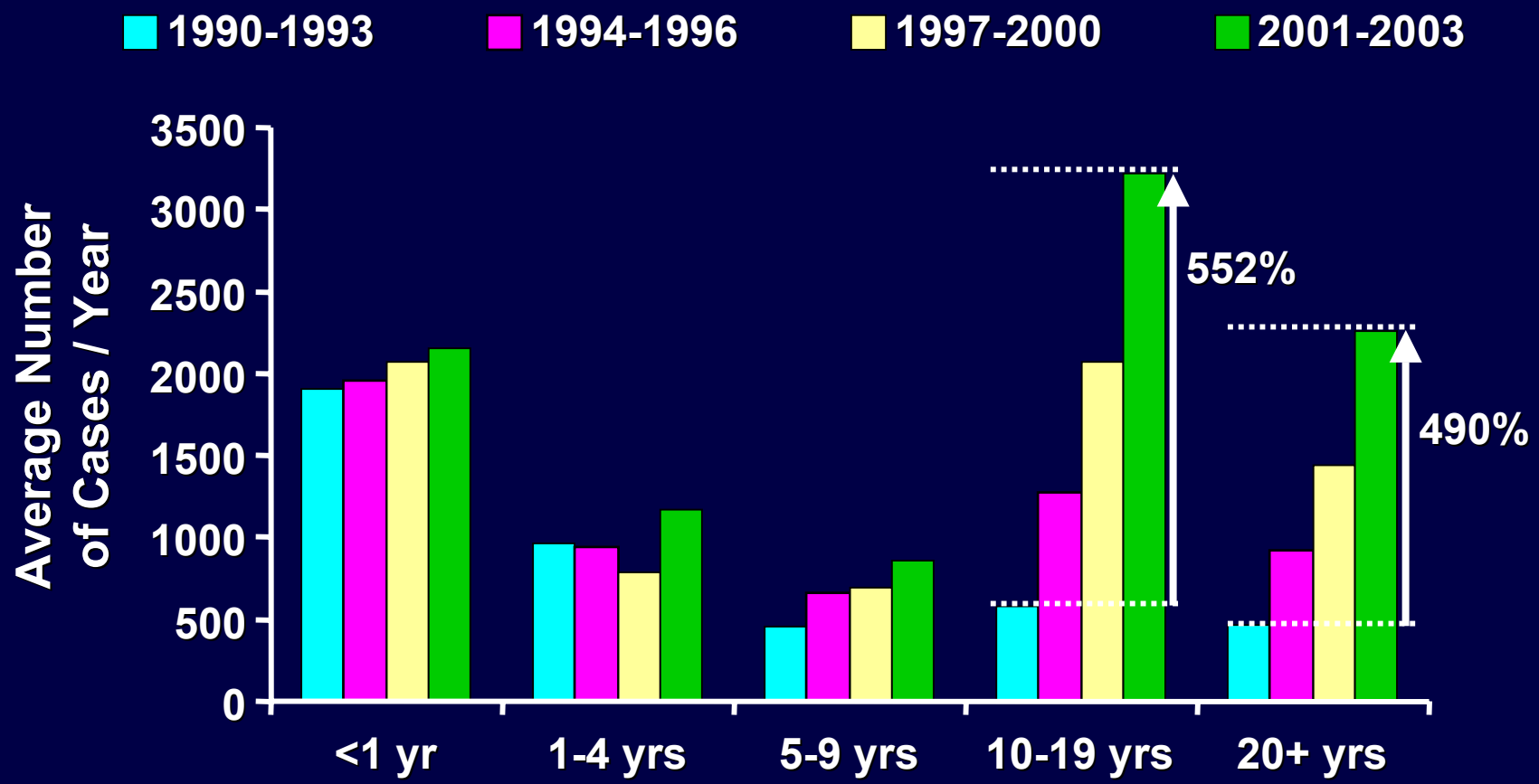
Reports of Pertussis
United States, 1980 – 2004



* Preliminary Data

CDC. MMWR 1997;46(54):71-80. Murphy T. Data on file, personal communication, 2001. MMWR 2000;50:1175. MMWR 2001;50(33):725. MMWR 2002;51:723. MMWR 2003;52:747. Bacterial Vaccine Preventable Disease Branch, National Immunization Program, 2004.

Reports of Pertussis in the U.S.



Centers for Disease Control and Prevention. *MMWR*. 2002;51:73-76;
Güriş et al. *Clin Infect Dis*. 1999;28:1230-1237.
National Immunization Program, Bacterial Vaccine Preventable Diseases Branch. Pertussis Surveillance Report, August 6, 2004

Prolonged Cough Illness in Adolescents and Adults Due to *Bordetella pertussis*

Source	Locale	Year(s)	% of cough illness
Nennig et al	San Francisco	1994-95	12
Strebel et al	Minn-St Paul	1995-96	13
Jackson et al	Seattle	1983-87	15
Jansen et al	San Diego	1993-94	17
Birbeback et al	Denmark	1995-97	17
Wright et al	Nashville	1992-94	21
Robertson et al	New S Wales	1985-86	26
Mink et al	Los Angeles	1986-89	26
Rosenthal et al	Chicago	1993-94	26
Wirsing v Köenig et al	Germany	1992-94	31
Schmitt-Grohé et al	Germany	1992-94	32
Vicent et al	Korea	1997-98	50
Gilberg et al	Paris	1999	52

Common Clinical Manifestations of Adolescent-Adult Pertussis

- **Cough 97% ≥ 3 weeks, 52% ≥ 9 weeks**
- **Paroxysms ≥ 3 weeks in 73%**
- **Whoop in 69%**
- **Post-tussive emesis in 65%**
- **Teens missed average 5 days of school; Adults missed average 7 days of work**
- **Average 14 days of disrupted sleep**

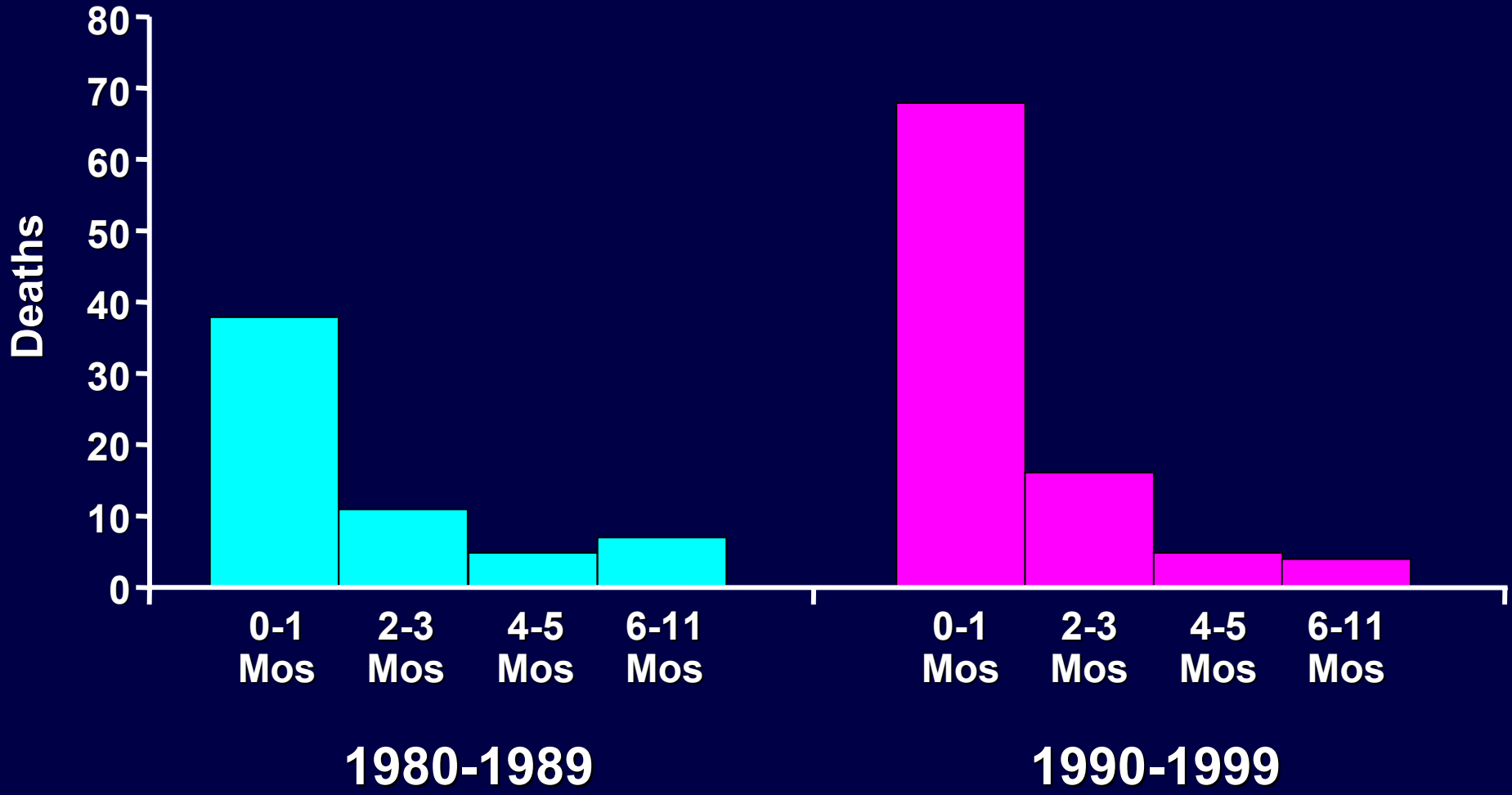
De Serres et al. *J Infect Dis*. 2000;182:174–9.

Complications of Adolescent – Adult Pertussis

- **Complications common in adolescents (16%) and adults (28%)**
- **Cyanosis found in 6% of adolescents and 9% of adults**
- **Pneumonia occurs in 2% of patients <30 years old and 5% to 9% of older patients**
- **Hospitalization of adolescents and adults at 1.4% and 3.5%, respectively**

De Serres et al. *J Infect Dis*. 2000;182:174–9.

Infant Pertussis Deaths by Decade 1980-1989 vs. 1990-1999



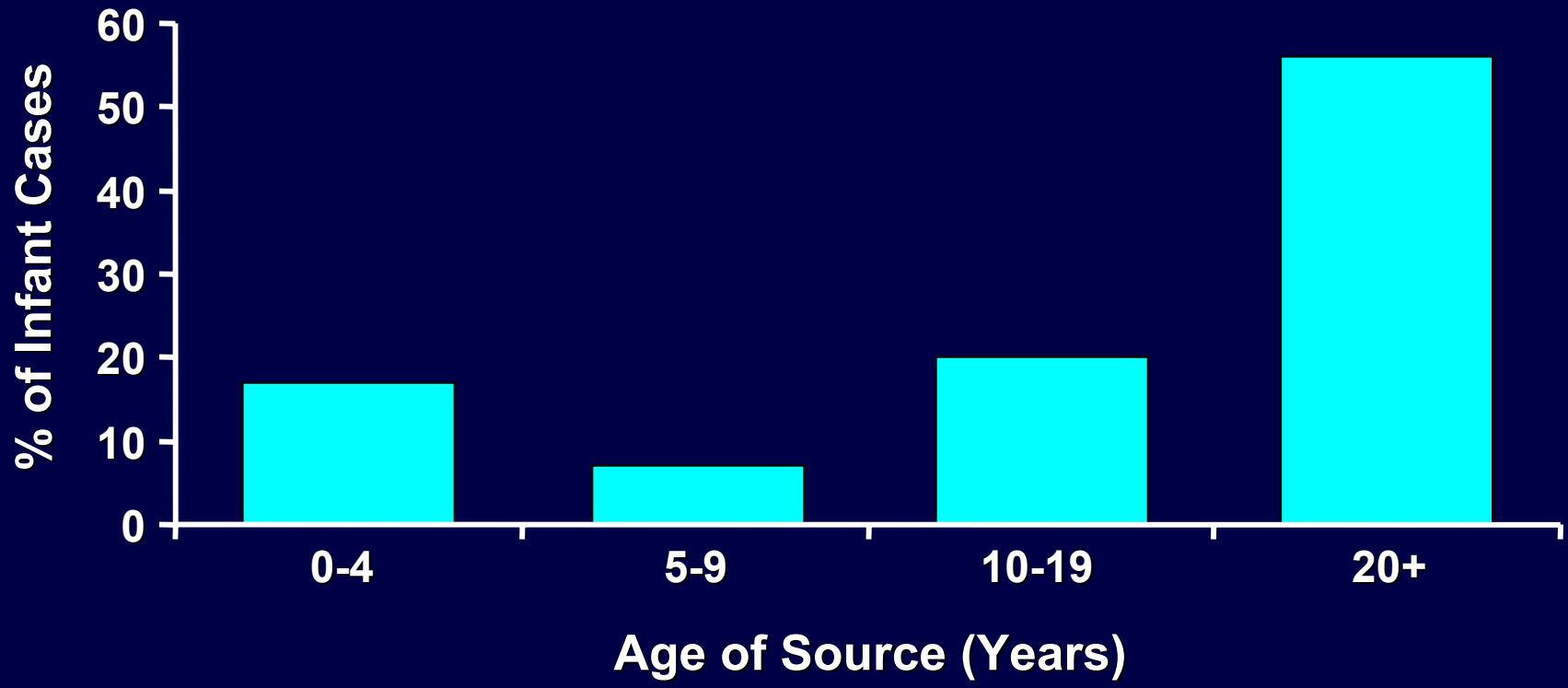
Vitek et al. *PIDJ.* 2003;22:628-634.

CDC Study – Infant Pertussis: Who Was the Source?

- 774 infant cases from 4 states
- 264 cases had source identified
- 75% family members
  - 43% mother
  - 20% father
  - 26% sibling
  - 11% grandparent
- 25% neighbor, friend, day care, and other

Bisgard, K. *PIDJ.* 2004;23:985-9.

Age of Pertussis Source* for Infants



*219 source-persons with known age

Bisgard, K. *PIDJ.* 2004;23:985-9.

Healthcare Professionals Involved in Transmission of Pertussis

Physicians	1912	Schwenkenbecher
Nurses	1972	Kurt et al
Physicians	1992	Etkind et al
Nurses	1995	Christie et al
Nurses	1997	Matlow et al
Nurses and Physicians	2004	CDC

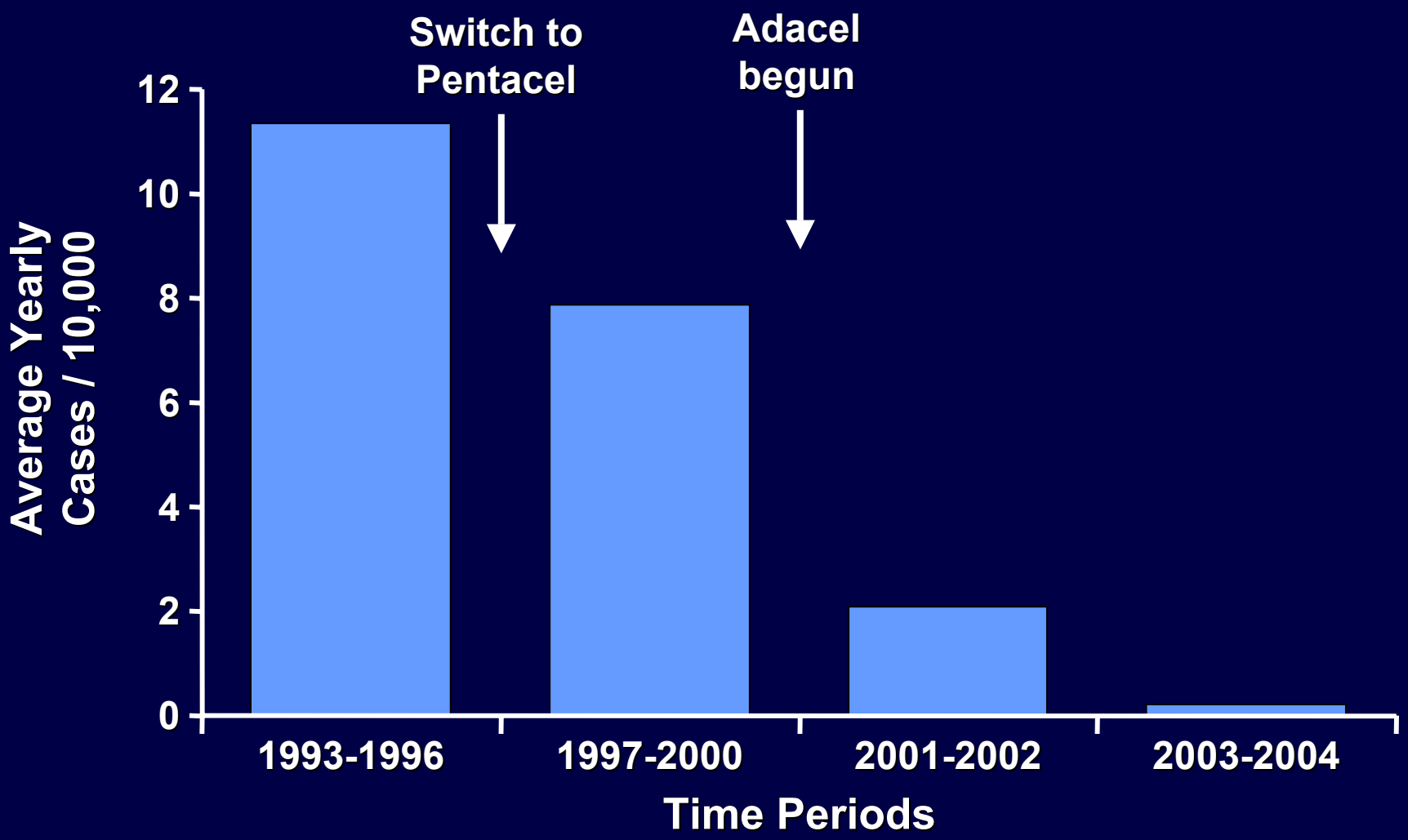
Schwenkenbecher, 1912;
Kurt et al. *JAMA.* 1972;221(3):264-7;
Etkind et al. *Am J Dis Child.* 1992;146:173-6;
Christie et al. *Infect Control Hosp Epidemiol.* 1995;16:556-63;
Matlow et al. *Infect Control Hosp Epidemiol.* 1997;18:715-16;
CDC. *MMWR*. 2004;54(03):67-71.

Adacel Experience in Canada

- **Adacel licensed in Canada – May 1999**
- **NACI issued a supportive statement, but at that time did not give a recommendation for universal routine use**
- **3 provinces or territories launched Adacel vaccination programs**

Health Canada. CCDR. 2000;26(ACS-1):1-8.

Pertussis Incidence and Vaccine Use, 1993 – 2004
Canada's Northwest Territories

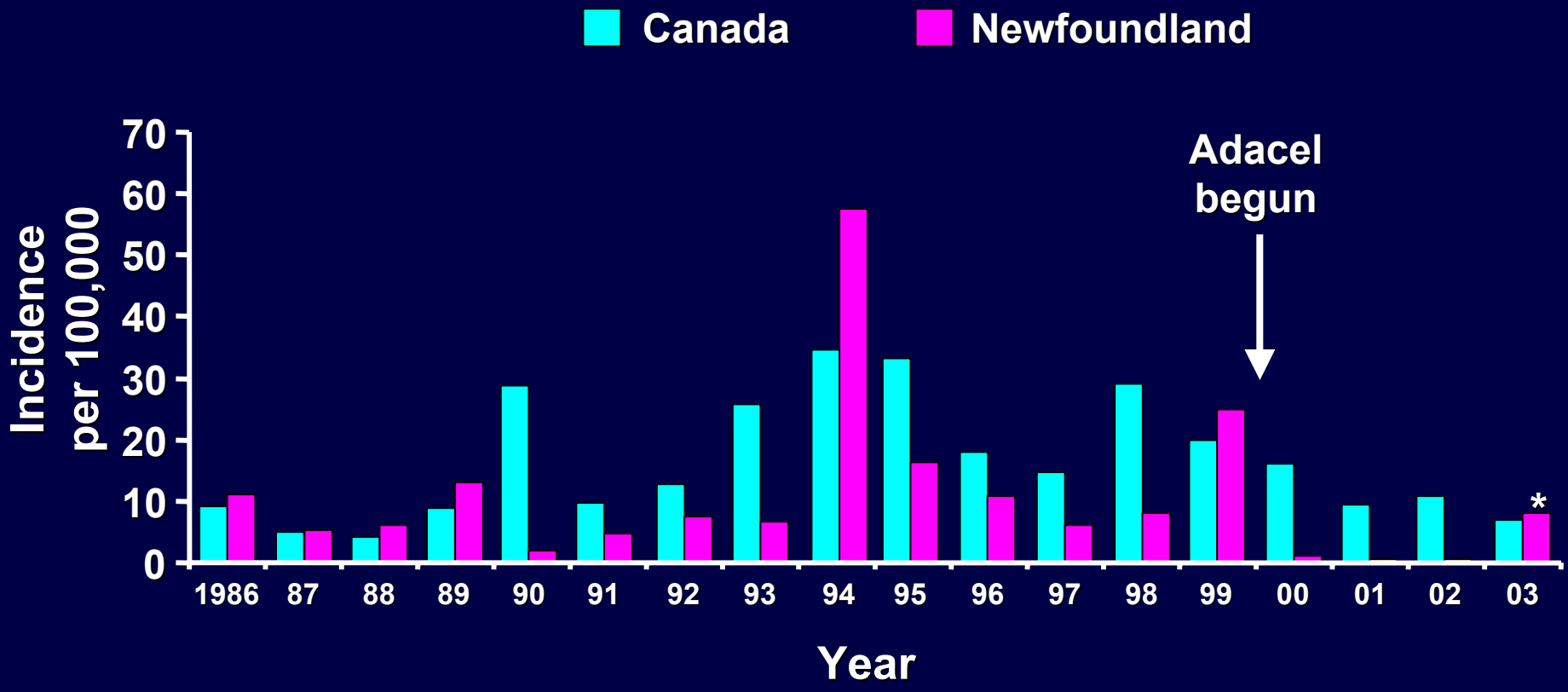


Kandola, K. Abstract in *Can J Infect Dis Med Microbiol.* 2004;15:351. Manuscript in preparation.

The Adacel Program in Newfoundland

- **Replaced Td in 1999 school year**
- **Adacel delivered in a Grade 9 (14 year olds) school-based program**
- **Approximately 25,000 doses given by June 2004**

Incidence of Pertussis, 1986 – 2003
Canada vs. Newfoundland



* Pertussis outbreak confined to persons not immunized with Adacel

Source: Data derived from CCDR Notifiable Disease Annual Summaries

Adacel Experience in Canada (cont'd)

- **NACI Adacel Recommendation – September 2003**
  - **A single booster dose should be administered to adolescents and adults in place of Td to protect against pertussis**
- **All remaining provinces and territories launched Adacel adolescent programs in 2003 - 2004**
- **Prince Edward Island conducted broad-based catch-up program – Fall 2004**
- **Quebec launched adolescent, adult, and "cocoon" program – September 2004**

Health Canada. CCDR. 2000;26(ACS-1):1-8; 2003;29(ACS-5):1-9.

Pertussis Epidemiology Summary

- **Reports of pertussis continue to increase dramatically**
- **Pertussis is common in adolescents and adults, causing significant morbidity and complications**
- **Adolescents and adults are important sources of pertussis transmission to vulnerable infants, in whom mortality is increasing**
- **Ongoing epidemiological surveillance data from Canada demonstrate potential of Adacel to control pertussis**

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Adacel Clinical Studies for US Licensure Studies, Age Groups, and Vaccinees

Study	Purpose	Age Group	N	Adacel
Td506	Large scale safety and immunogenicity, vs. Td	11-64 yr	4461	3017
Td505	Lot Consistency	11-17 yr	1806	1806
Td501	Interaction with HB	11-14 yr	403	403
Td502	Interaction with Influenza	19-64 yr	696	696
TC9704	Lot Consistency	12-54 yr	600	449
Td9707	Adacel vs Td, aP	19-60 yr	370	244
Td9805	Interaction with HB	11-13 yr	269	269
			Total number of Adacel recipients:	**6884**

Overall Summary: Safety and Immunogenicity Populations

Study	Planned Subjects	Enrolled	Safety	Immuno
Td506	4400	4480	4301	2296
Td505	1800	1811	1806	1056
Td501	410	410	403	312
Td502	690	720	696	678
Total	7300	7421	7206	4342

Of the safety population, 5841 received Adacel and 1365 received Td.

Overall Summary: Safety and Immunogenicity Populations

Study	Planned Subjects	Enrolled	Safety	Immuno
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Td505	1800	1811	1806	1056
Td501	410	410	403	312
Td502	690	720	696	678
Total	7300	7421	7206	**4342**

Of the immunogenicity population, 3316 received Adacel and 1026 received Td.

Td505 and Td506 Distribution of ITT Populations By Gender and Race/Ethnicity

	Adolescents (N = 3782) %	Adults (N = 2325) %	Total (N = 6107) %
Gender			
Female	49.3	64.0	54.9
Male	50.7	36.0	45.1
Race/Ethnicity			
Caucasian	86.1	84.9	85.7
Black	9.1	9.6	9.3
Hispanic	2.0	3.1	2.4
Asian	1.2	1.3	1.2
Other	1.6	1.0	1.4

Measuring Immunogenicity

Immunological Endpoints

- **Seroprotection Rates**
  - % of participants who develop a benchmark (eg, protective) diphtheria or tetanus titer
  - Primary outcome measure in all of the core clinical trials
- **Booster Rates**
  - % of participants who develop a defined increase in titer, stratified by pre-titer
  - Primary outcome measure in one core clinical trial

Measuring Immunogenicity (2)

Immunological Endpoints

- **Geometric Mean Titers**
  - Normalized average of the post-immunization titers
  - Primary pertussis outcome measure; descriptive for diphtheria and tetanus
- **Reverse Cumulative Distribution Curves**
  - Graphical presentation of the antibody distribution of the entire studied population
  - Descriptive only

Measuring Immunogenicity

Endpoint	Non-inferiority or equivalency criteria using 90% or 95% CI
Seroprotection and Booster Rates	Difference in rates between groups at 10% margin
GMTs	GMTs ratio between groups at 1.5 margin

Adacel Link to Efficacy

Adacel link to efficacy: Td506 vs. Sweden I efficacy trial

- **Sweden I was an NIH-sponsored, prospective, randomized, double-blinded, placebo-controlled and whole-cell-pertussis-controlled efficacy trial in Sweden 1992-1995**
  - **Infants received 3 doses of Daptacel at 2, 4, 6 months of age**
  - **85% efficacy vs. WHO-defined classic pertussis; 78% efficacy vs. any pertussis (lab-confirmed, ≥ 1 day of cough)**
- **Pertussis immunogenicity results following 1 dose of Adacel in US pivotal trial Td506 were compared to those following 3 doses of Daptacel in Sweden I Efficacy Trial**
- **Sera from Adacel recipients and stored sera from infants in the Sweden I Efficacy Trial were tested contemporaneously in same laboratory, under same conditions, using the same validated assay**

Rationale for Serologic Bridge to Sweden I Efficacy Trial Data

- **Adacel and Daptacel are the same vaccine, except that PT and D toxoids have been reduced in Adacel to levels appropriate for adolescent-adult use**
- **Household contacts (representing all ages, from infants to older adults) who developed clinical pertussis had PRN and agglutinin titers below the same cut-off level**
- **Immunologic correlates of protection from one population have been used routinely to license booster vaccines in a different age group**

Rationale for Serologic Bridge to Sweden I Efficacy Trial Data

- **The VRBPAC meeting of June 5, 1997 was devoted to the question of licensing criteria for adolescent-adult aP vaccines. The committee endorsed licensure based on a serologic bridge to infant efficacy data:**
  - **Question 1: Can demonstration of efficacy of a given acellular pertussis vaccine administered as a primary series to infants serve as a basis for efficacy of that vaccine when administered as a booster dose to adolescents and adults? YES**
  - **Question 2: Is demonstration of comparable antibody responses in adults/adolescents and infants an appropriate indicator that the different age groups respond to the vaccine in equivalent manners? …In other words, can we use antibodies to bridge between the two age groups, as we have done between the primary series and the booster series? YES**

Measuring Immunogenicity

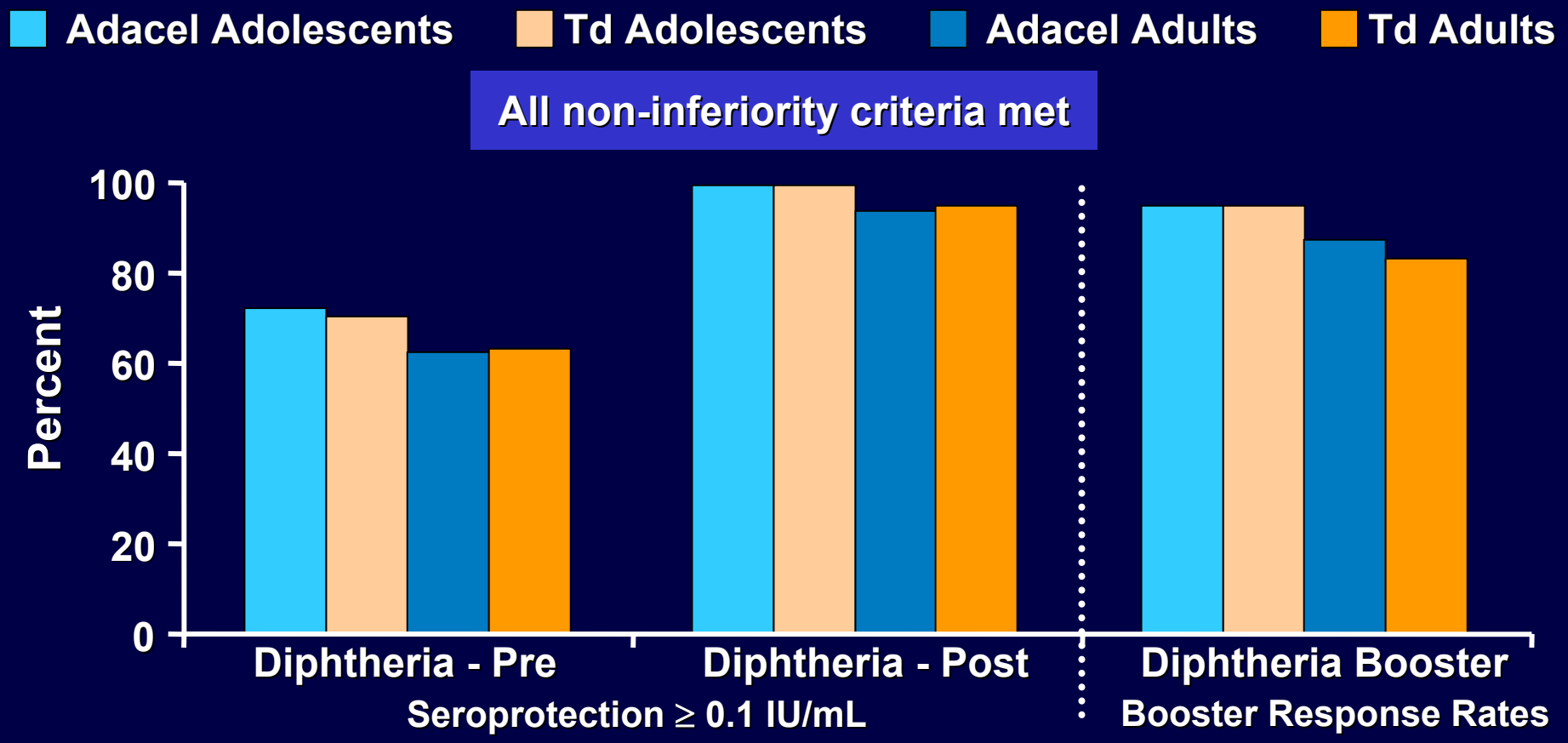
Results to be Presented

- **Td506: Comparative trial in adolescents and adults**
- **Td505: Lot consistency trial in adolescents**
- **Td501: Concomitant Adacel and hepatitis B trial in adolescents**
- **Td502: Concomitant Adacel and influenza trial in adults**

Td506: Comparative Clinical Trial vs. Td in Adolescents and Adults

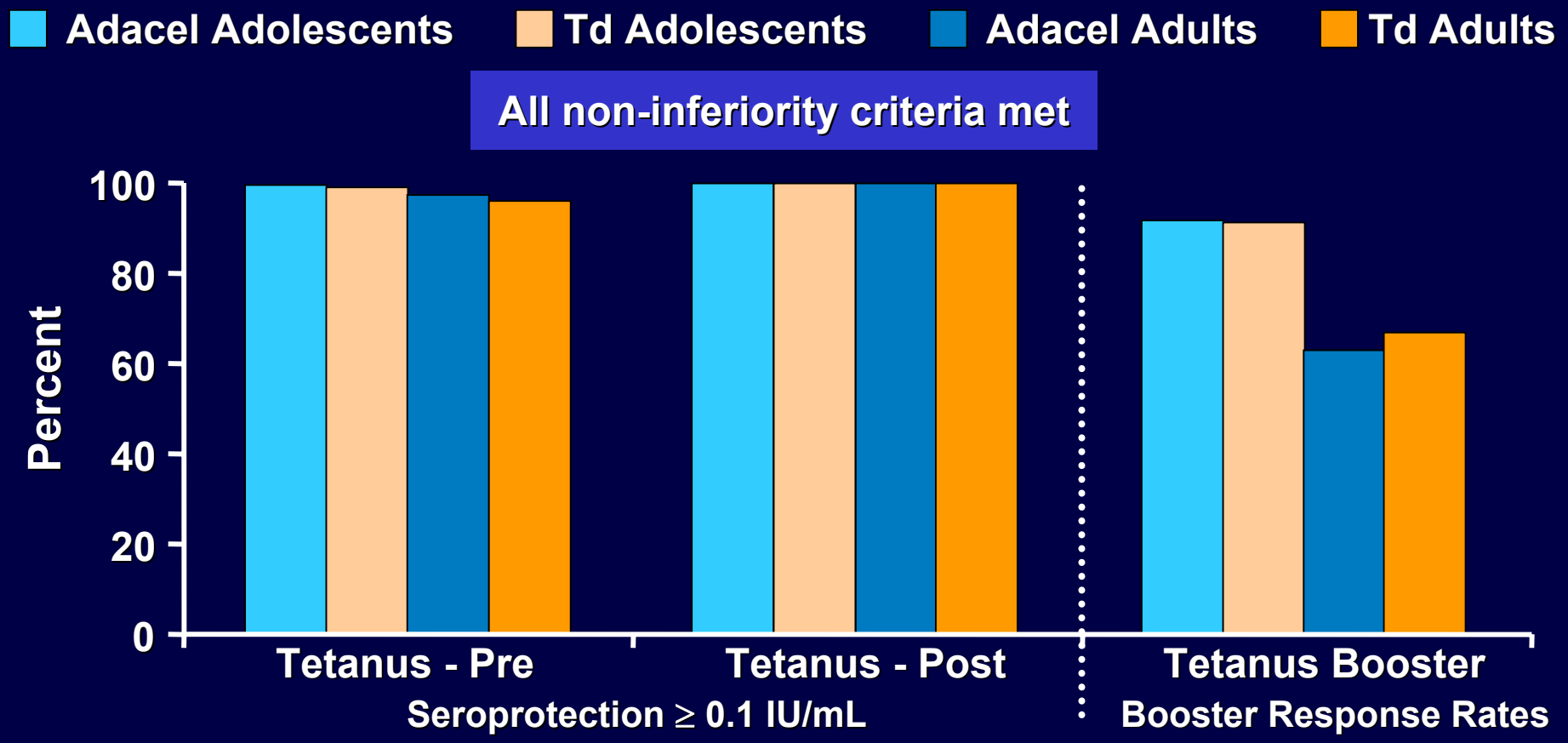
- **Multicenter, large scale immunogenicity and safety study, 39 US sites, 4461 vaccinees**
- **Randomized, modified double blind study; age stratified:**
  - **11-13**
  - **14-17**
  - **18-28**
  - **29-48**
  - **49-64 years**

Td506: Diphtheria Seroprotection ≥ 0.1 IU/mL and Booster Rates



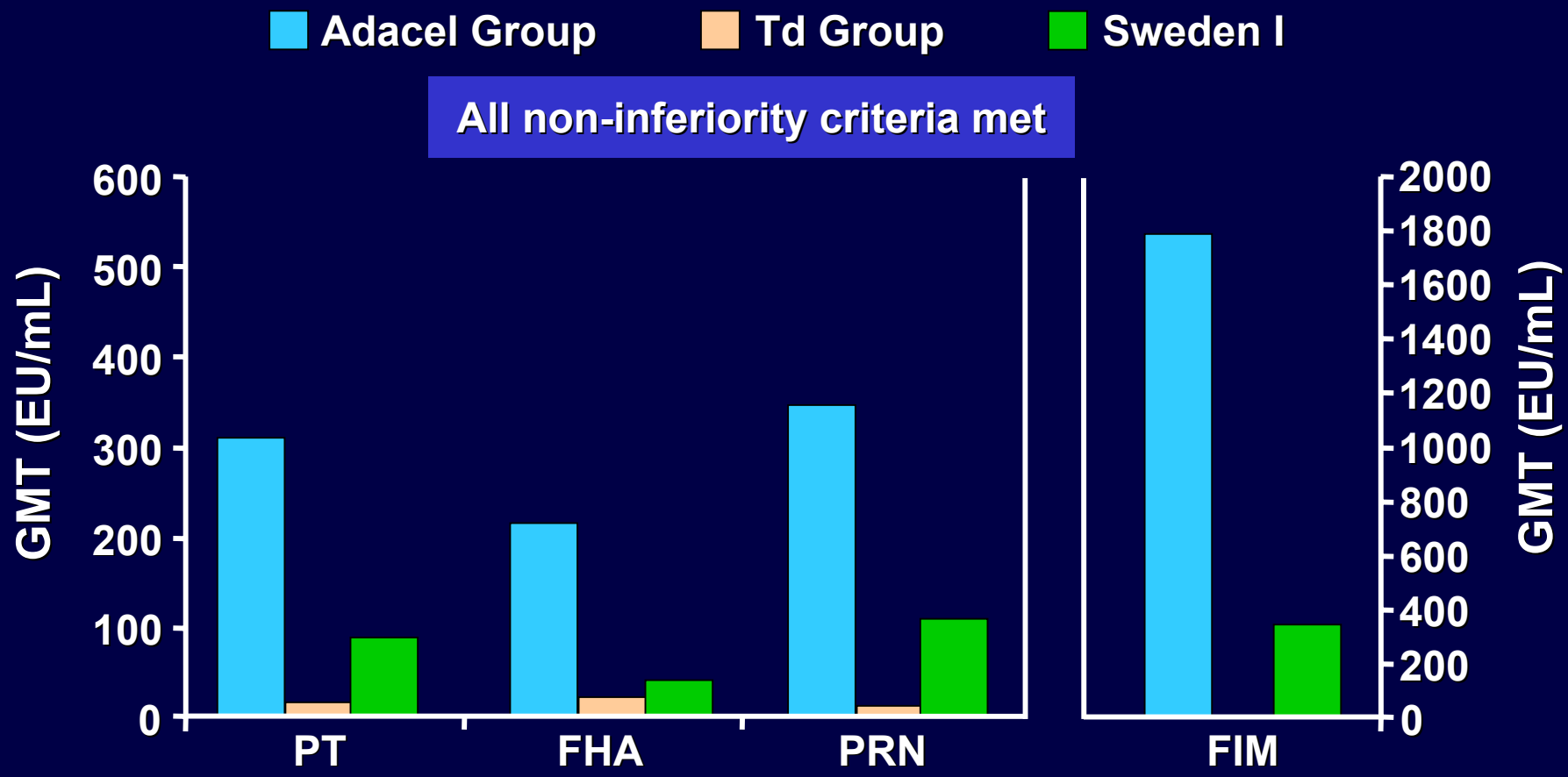
Adacel Adol	382 of 527, 72.5%	526 of 527, 99.8%	501 of 527, 95.1%
Td Adolescents	364 of 515, 70.7%	515 of 516, 99.8%	489 of 515, 95.0%
Adacel Adults	464 of 741, 62.6%	697 of 741, 94.1%	646 of 739, 87.4%
Td Adults	321 of 507, 63.3%	482 of 507, 95.1%	422 of 506, 83.4%

Td506: Tetanus Seroprotection ≥ 0.1 IU/mL and Booster Rates



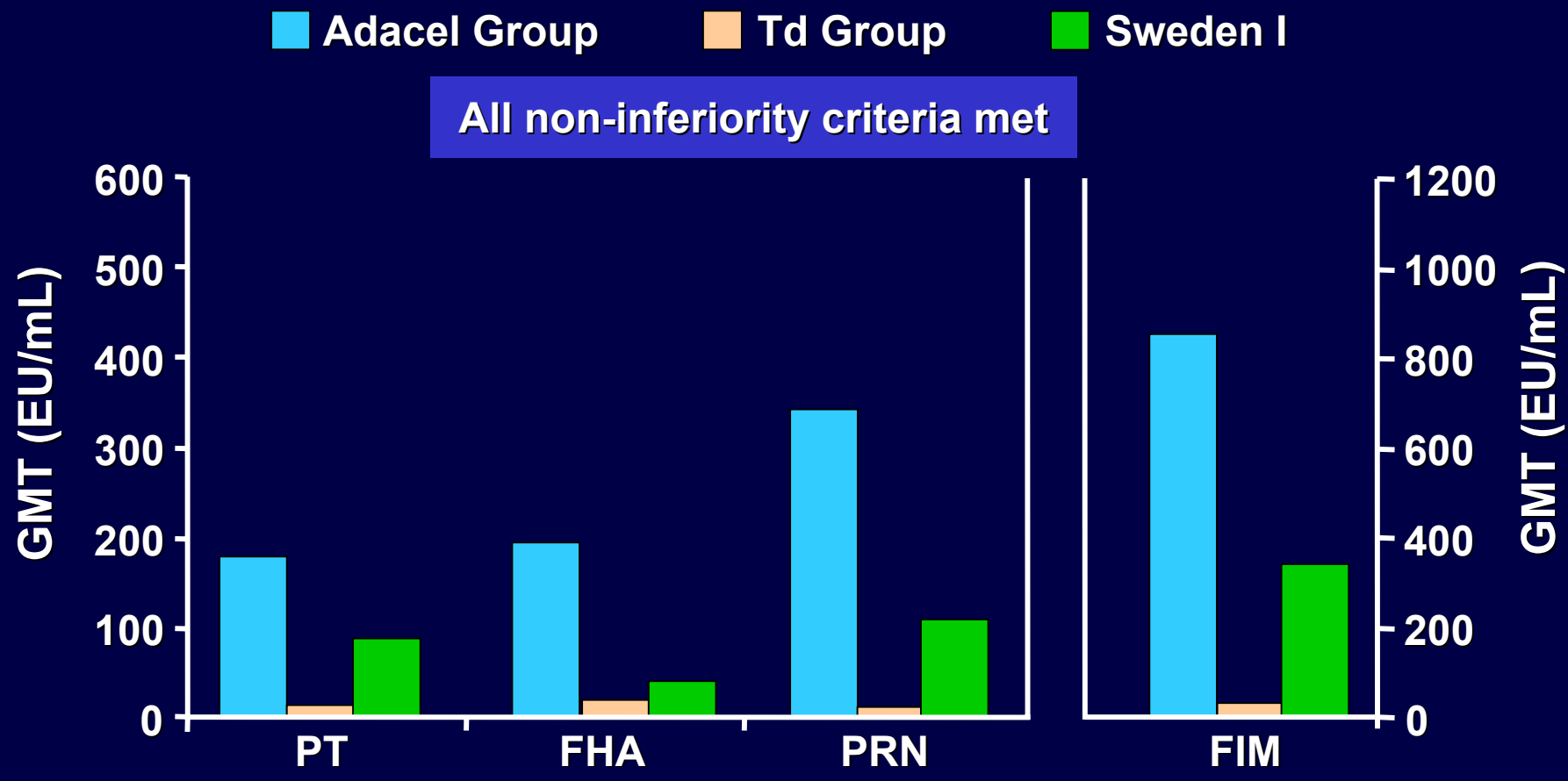
Adacel Adol	525 of 527, 99.6%	527 of 527, 100%	483 of 527, 91.7%
Td Adolescents	512 of 516, 99.2%	516 of 516, 100%	471 of 516, 91.3%
Adacel Adults	723 of 743, 97.3%	742 of 742, 100%	468 of 742, 63.1%
Td Adults	488 of 509, 95.9%	508 of 509, 99.8%	340 of 509, 66.8%

Td506: Pertussis Post-Vaccination GMTs, Adolescents, vs. Sweden I



Adacel	309.3	214.8	344.5	1792.4
Td	15.6	20.9	11.7	28.8
Sweden I	86.6	40.0	108.1	341.1

Td506: Pertussis Post-Vaccination GMTs, Adults, vs. Sweden I



Adacel	178.8	192.9	341.9	852.7
Td	13.2	19.3	11.7	31.7
Sweden I	86.6	40.0	108.1	341.1

Td506: Immunogenicity Conclusions

- **Adacel vaccine is**
  - **Non-inferior to Td vaccine for diphtheria and tetanus immune responses**
  - **Highly immunogenic with respect to pertussis responses**
  - **Non-inferior to Sweden I for pertussis responses**

Measuring Immunogenicity

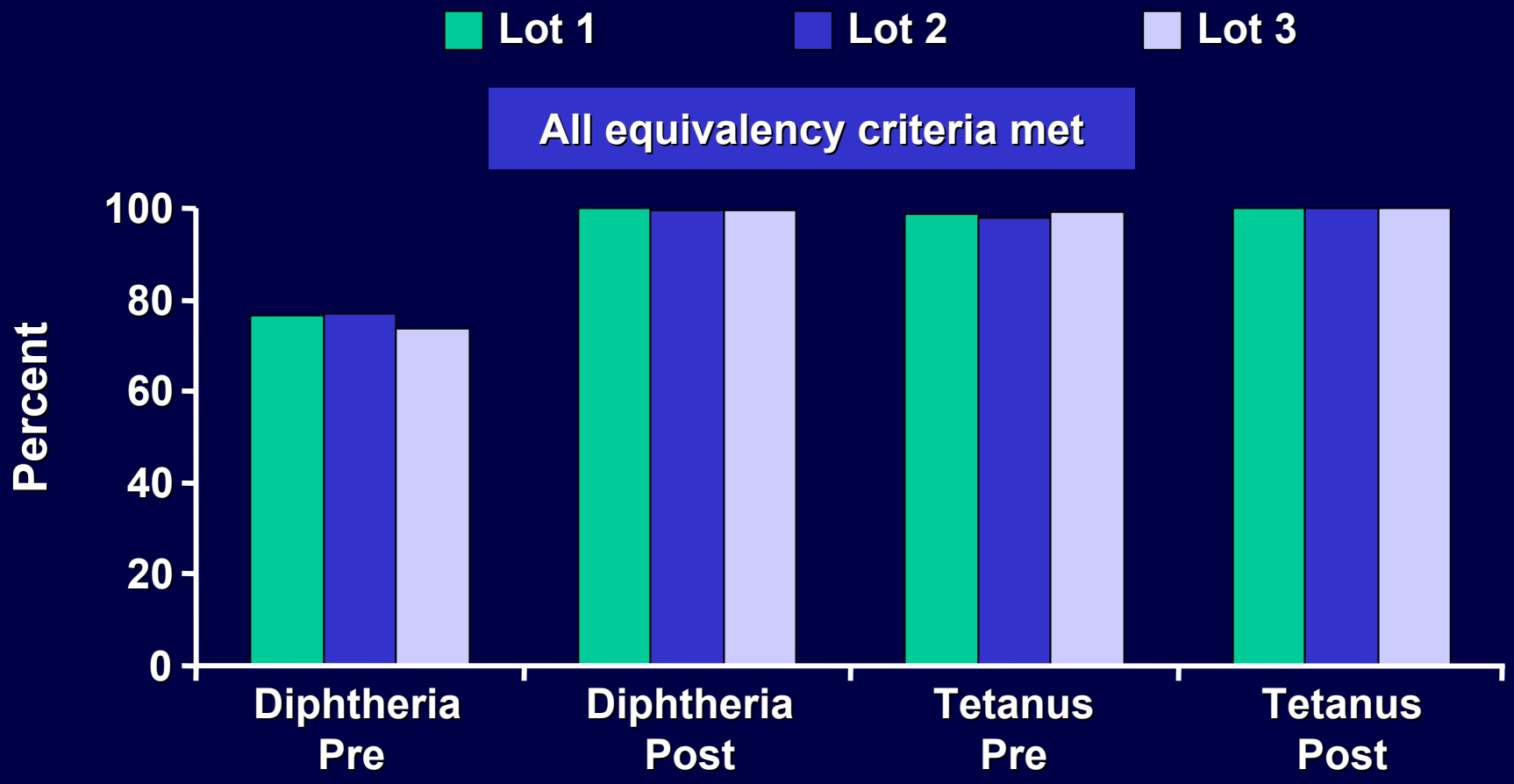
Results to be Presented

- **Td506: Comparative trial in adolescents and adults**
- **Td505: Lot consistency trial in adolescents**
- **Td501: Concomitant Adacel and hepatitis B trial in adolescents**
- **Td502: Concomitant Adacel and influenza trial in adults**

Td505: Lot-Consistency Trial

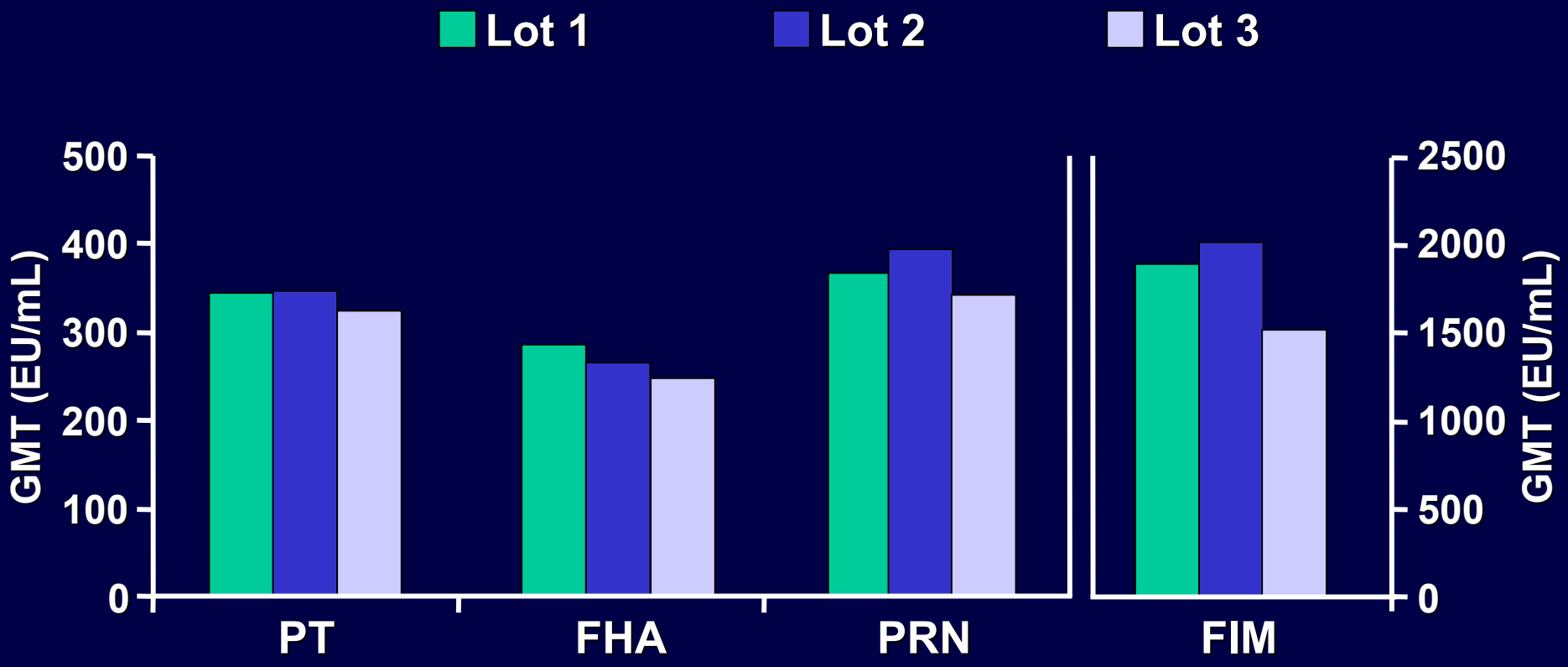
- **Multicenter study, 18 US sites, in 1806 adolescents 11-17 years**
- **Age-stratified, randomized, modified double blind study**

Td505: Diphtheria and Tetanus Seroprotection at ≥ 0.1 IU/mL



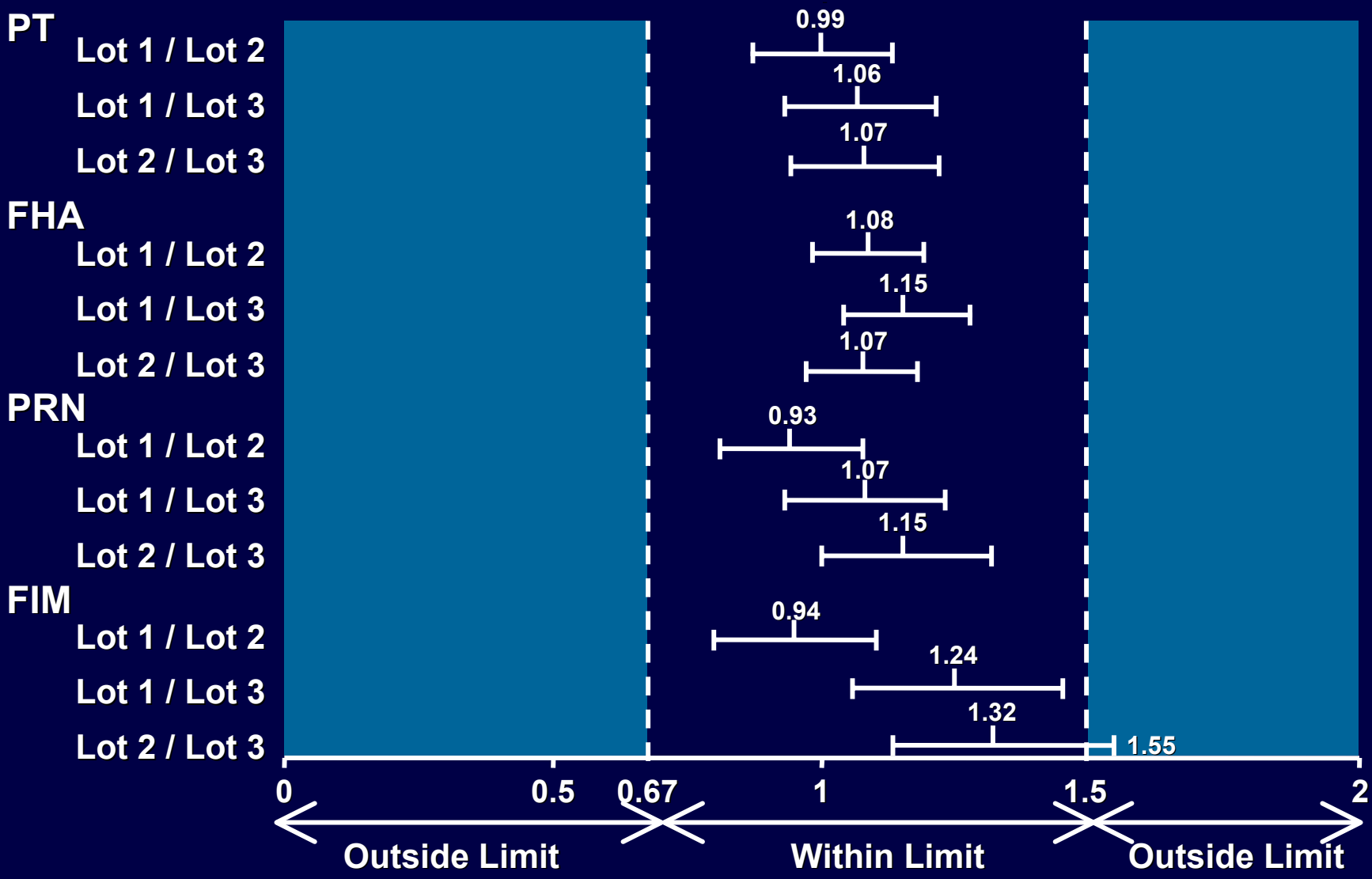
Lot 1	269 of 351, 76.6%	351 of 351, 100%	345 of 350, 98.6%	351 of 351, 100%
Lot 2	269 of 350, 76.9%	347 of 349, 99.4%	342 of 349, 98%	350 of 350, 100%
Lot 3	262 of 355, 73.8%	352 of 353, 99.7%	352 of 355, 99.2%	353 of 353, 100%

Td505: Pertussis GMTs Post-Vaccination

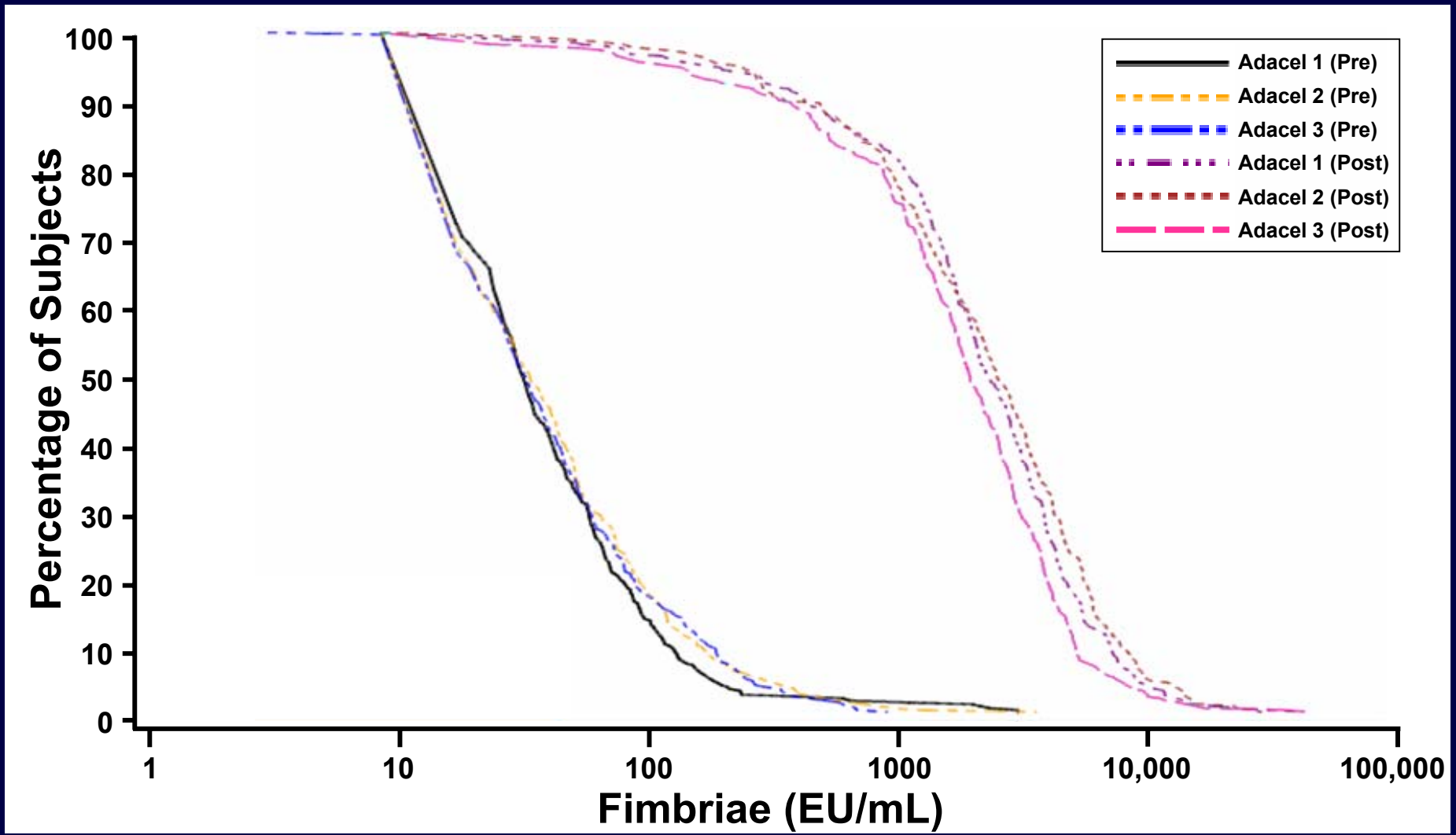


Lot 1	343.7	285.1	366.1	1901.6
Lot 2	347.4	265	394.7	2025.4
Lot 3	323.9	247.8	343.2	1528.8

Td505: Equivalence of Pertussis GMTs 90% CI of Ratios of Lots



Td505: Pre- and Post-Immunization FIM Titers for 3 Lots of Adacel Vaccine



Td505: Lot Consistency Study Conclusions

Equivalency demonstrated for:

- **Diphtheria Seroprotection and Booster Rates and GMTs**
- **Tetanus Seroprotection and Booster Rates and GMTs**
- **Pertussis GMTs**
  - **PT**
  - **FHA**
  - **PRN**
  - **2 of 3 FIM comparisons (third was borderline)**

Measuring Immunogenicity

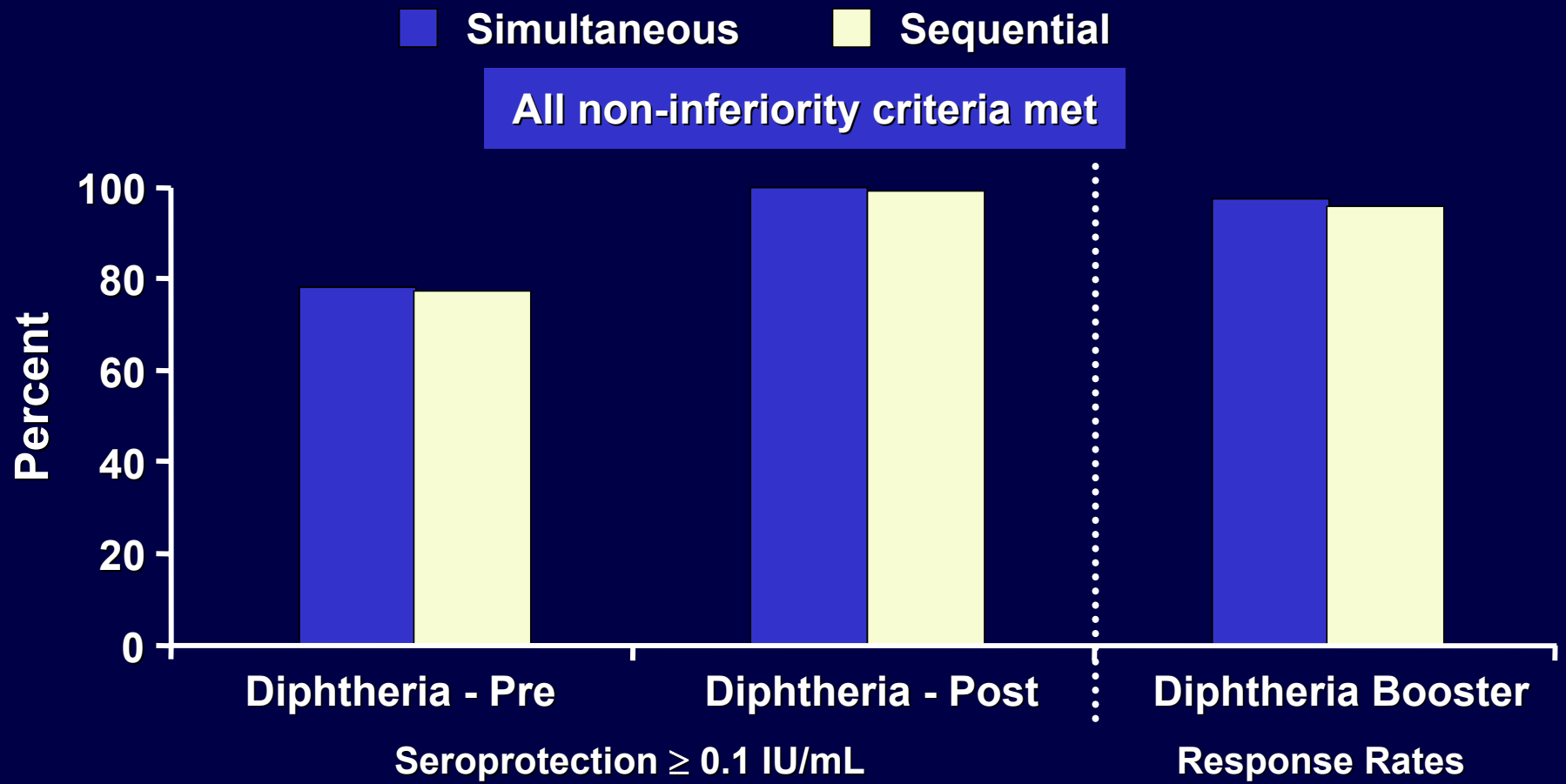
Results to be Presented

- **Td506: Comparative trial in adolescents and adults**
- **Td505: Lot consistency trial in adolescents**
- **Td501: Concomitant Adacel and hepatitis B trial in adolescents**
- **Td502: Concomitant Adacel and influenza trial in adults**

Td501: Co-Administration with HB Vaccine

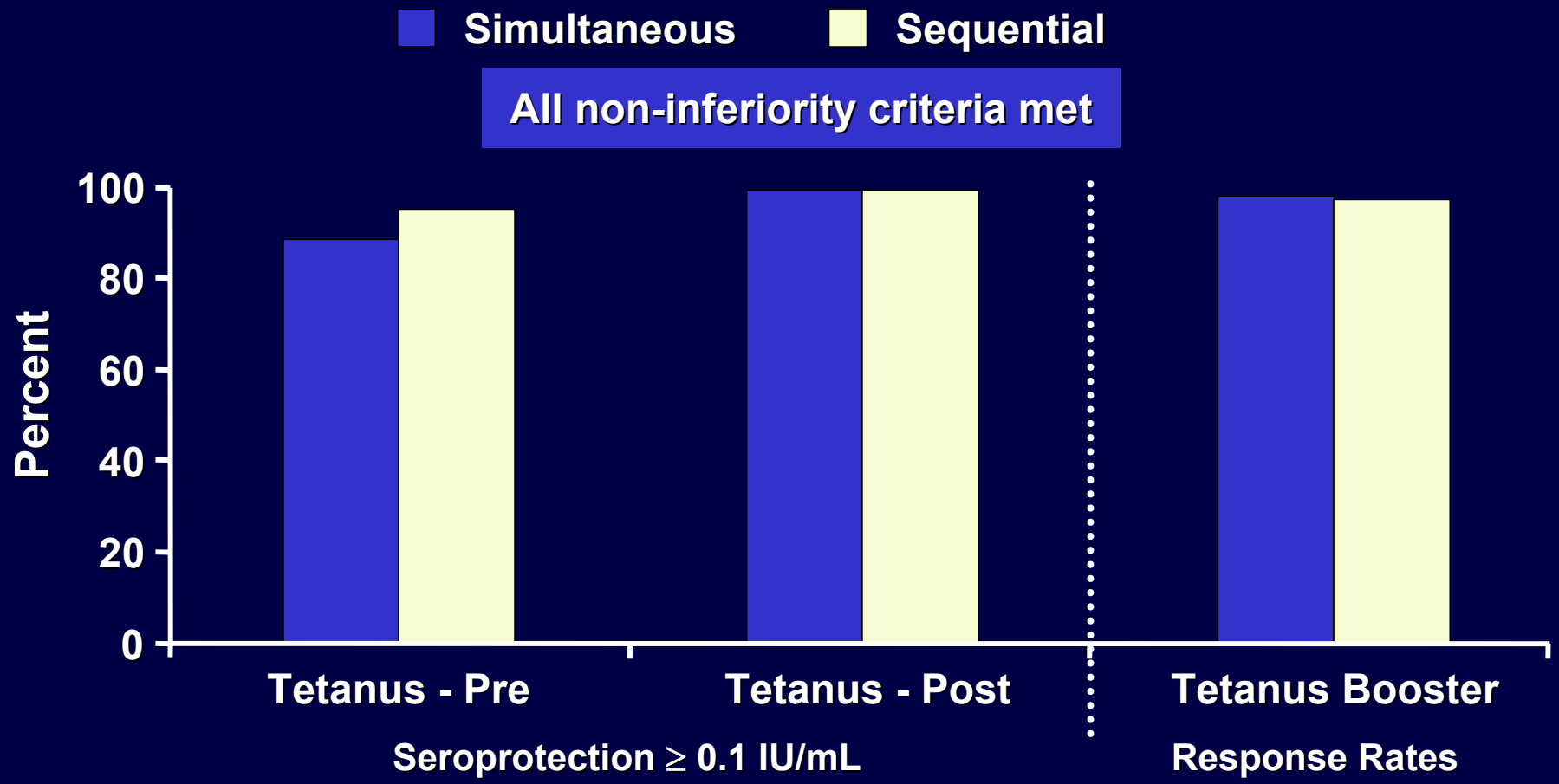
- **Multicenter, randomized, controlled, open-label study in 403 adolescents aged 11-14 years**
- **Concomitant Adacel+HB vaccine (n = 202) vs. Adacel, then HB vaccine 1 month later (n = 201)**
- **Objective: Demonstrate non-inferiority of simultaneous vs. sequential administration of Adacel and HB vaccine**

Td501: Adacel and HB, Diphtheria Seroprotection ≥ 0.1 IU/mL and Booster Rates



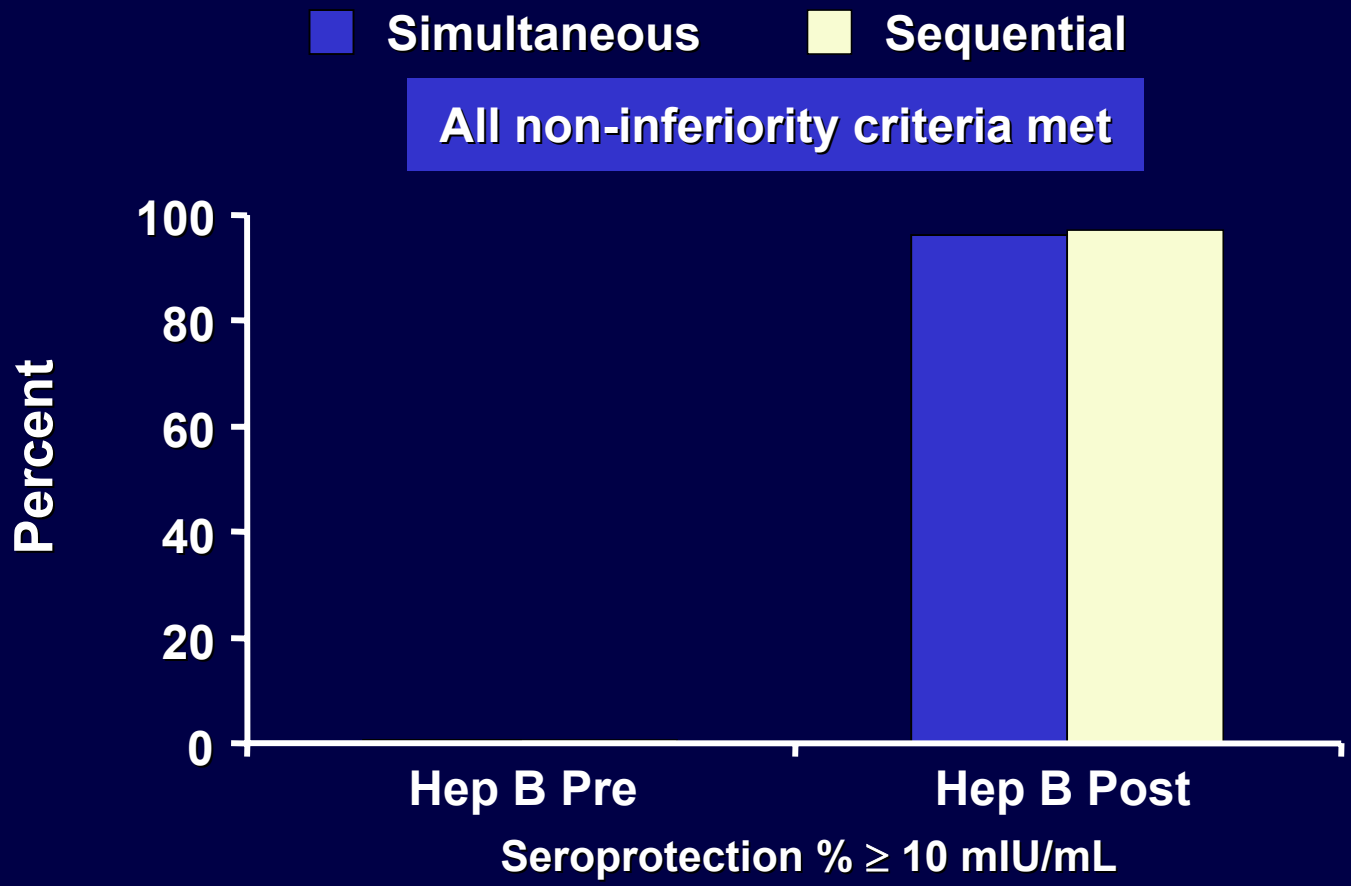
Simultaneous	126 of 161, 78.3%	161 of 161, 100%	157 of 161, 97.5%
Sequential	117 of 151, 77.5%	150 of 151, 99.3%	145 of 151, 96%

Td501: Adacel and HB, Tetanus Seroprotection ≥ 0.1 IU/mL and Booster Rates



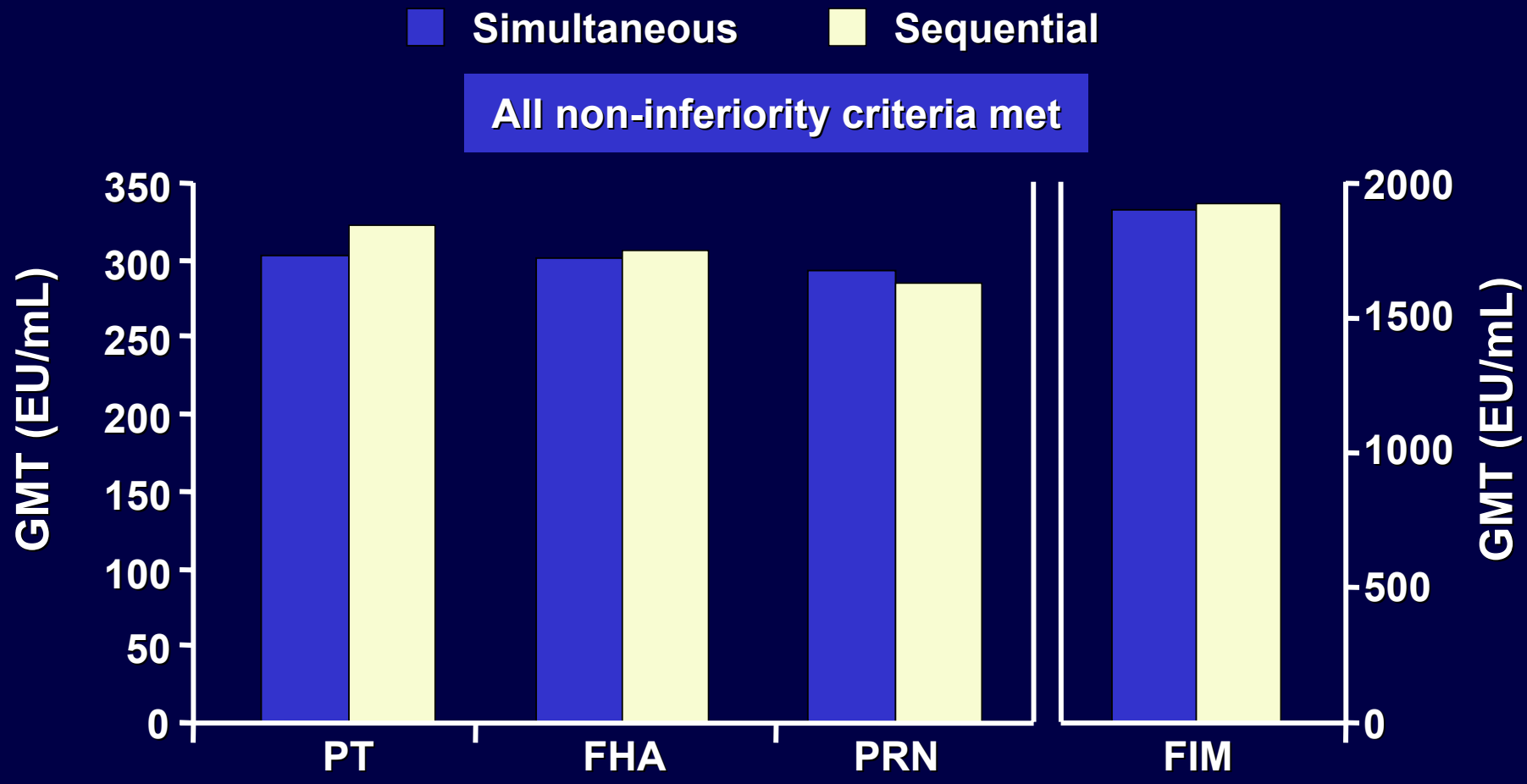
Simultaneous	144 of 161, 89.4%	161 of 161, 100%	159 of 161, 98.8%
Sequential	145 of 151, 96%	151 of 151, 100%	148 of 151, 98%

Td501: Adacel and HB
HB Seroprotection ≥ 10 mIU/mL



Simultaneous	1 of 161, 0.6%	155 of 161, 96.3%
Sequential	1 of 151, 0.7%	146 of 150, 97.3%

Td501: Adacel and HB, Pertussis GMTs



Simultaneous	303.5	301.5	292.9	1906.4
Sequential	321.6	305.4	284.6	1926.7

Td501: Co-Administration with HB Immunogenicity Conclusions

- **Adacel may be administered concomitantly with hepatitis B vaccine**
- **Simultaneous and sequential vaccination resulted in comparable immune responses for:**
  - **Diphtheria and Tetanus**
  - **Pertussis**
  - **Hepatitis B**

Measuring Immunogenicity

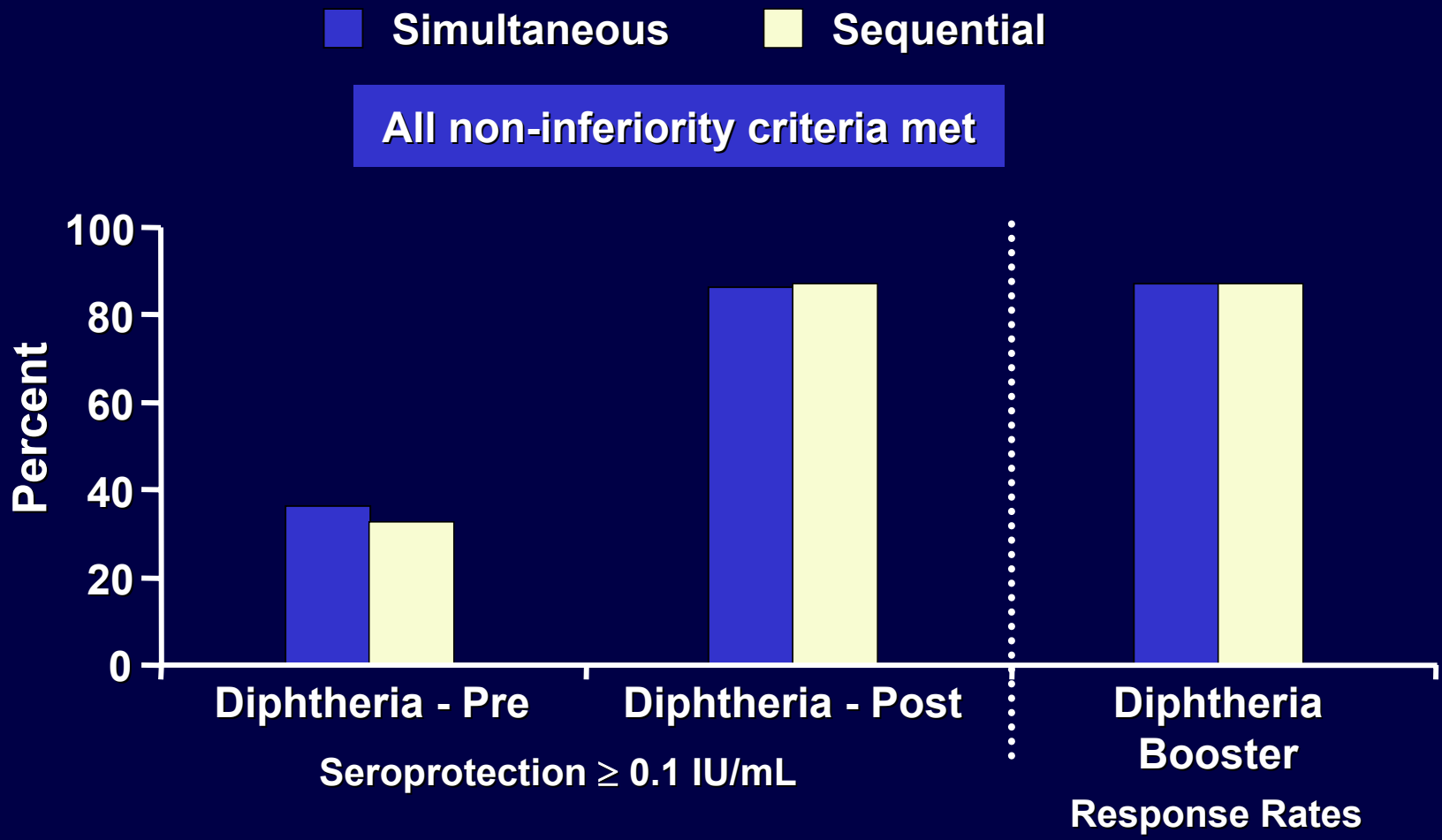
Results to be Presented

- Td506: Comparative trial in adolescents and adults
- Td505: Lot consistency trial in adolescents
- Td501: Concomitant Adacel and hepatitis B trial in adolescents
- **Td502: Concomitant Adacel and influenza trial in adults**

Td502: Co-Administration with Flu Vaccine

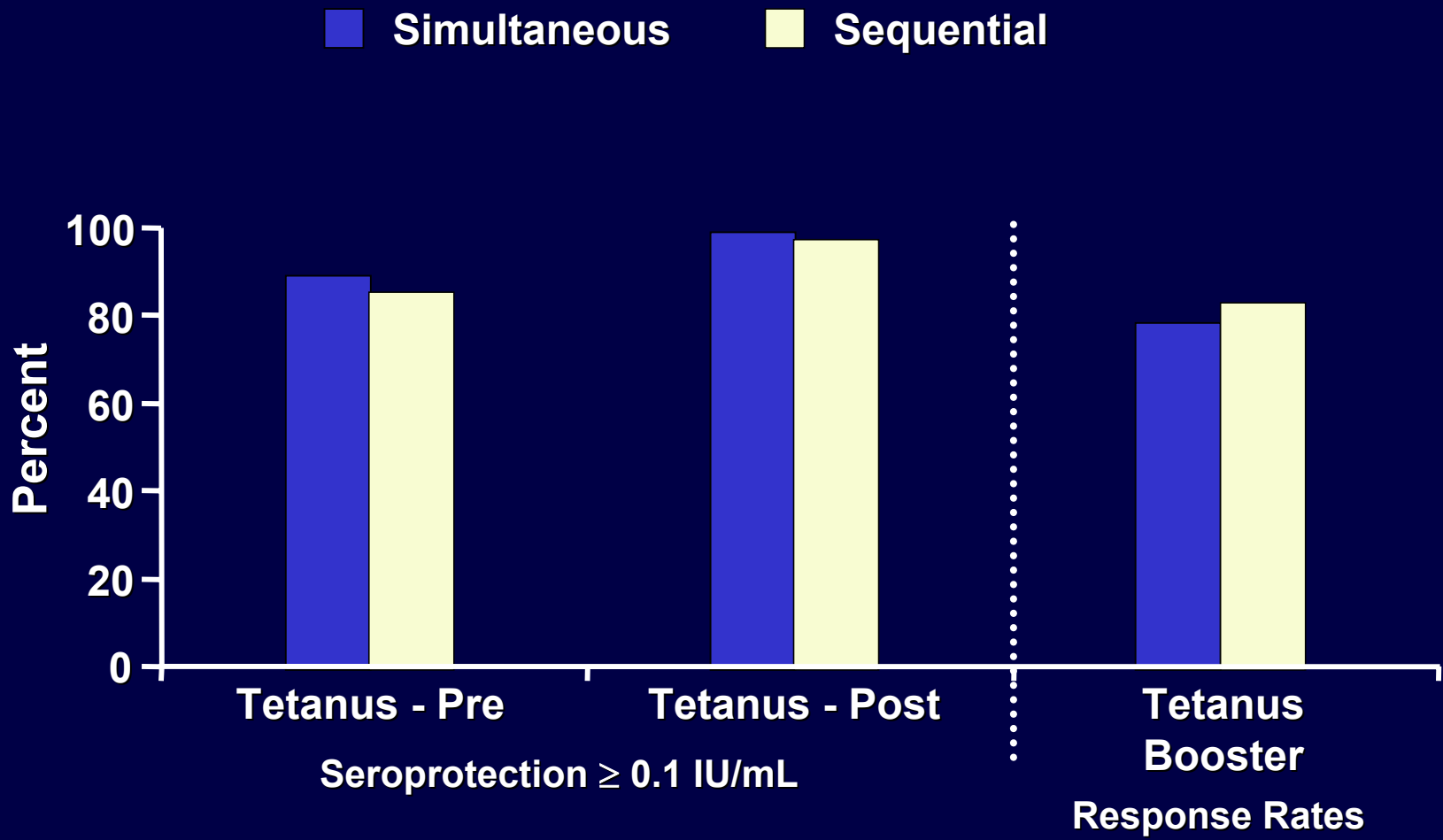
- **Multicenter, randomized, controlled, open label study in 696 adults aged 19-64 years**
- **Concomitant Adacel+Fluzone (n = 356) vs. Fluzone, then Adacel 1 month later (n = 340)**
- **Objective: Demonstrate non-inferiority of simultaneous vs. sequential administration of Adacel and Fluzone**

Td502: Adacel and Fluzone, Diphtheria Seroprotection ≥ 0.1 IU/mL and Booster Rates



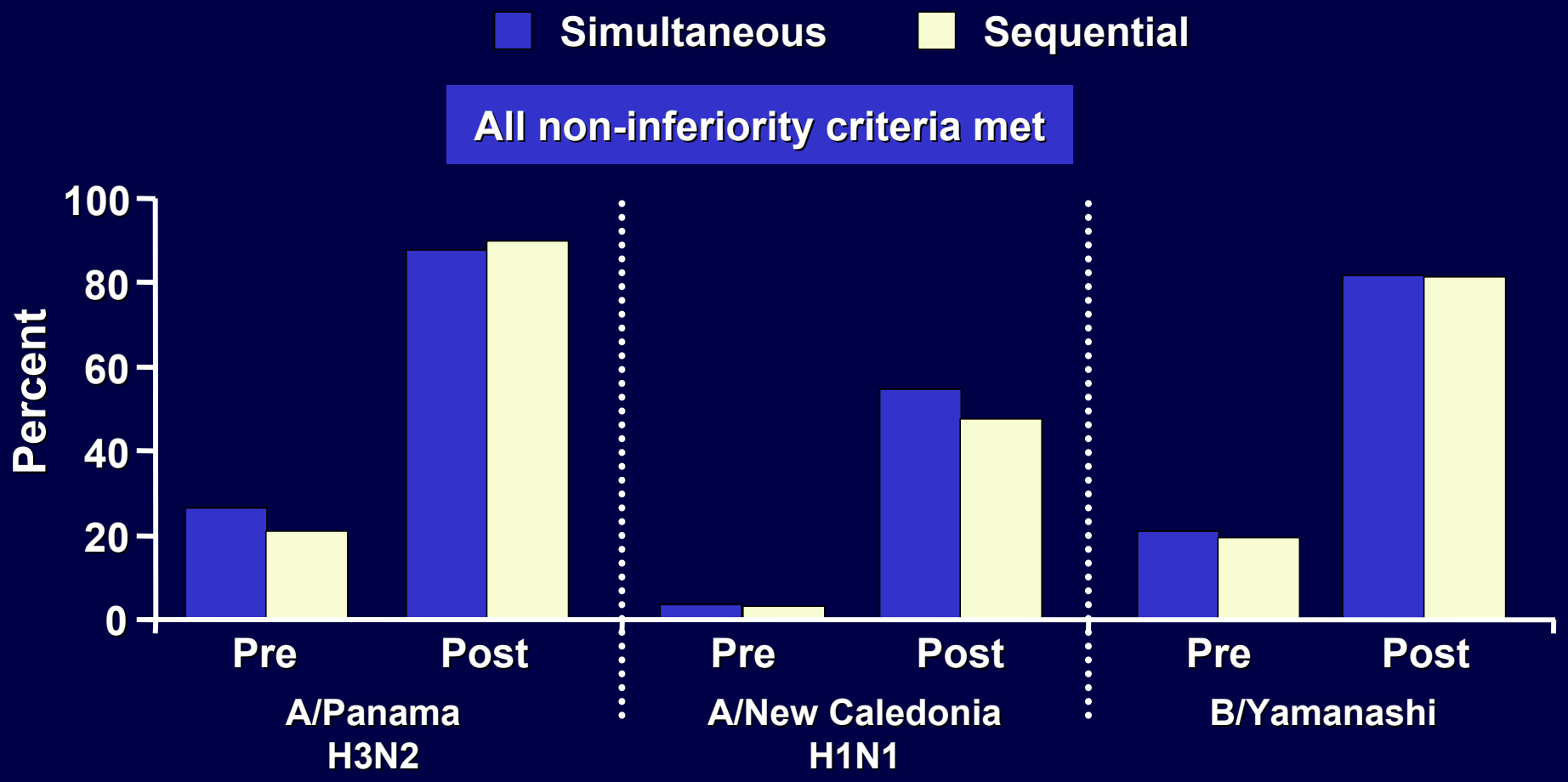
Simultaneous	129 of 354, 36.4%	305 of 354, 86.2%	308 of 354, 87.0%
Sequential	105 of 323, 32.5%	282 of 324, 87.0%	281 of 323, 87.0%

Td502: Adacel and Fluzone, Tetanus Seroprotection ≥ 0.1 IU/mL and Booster Rates



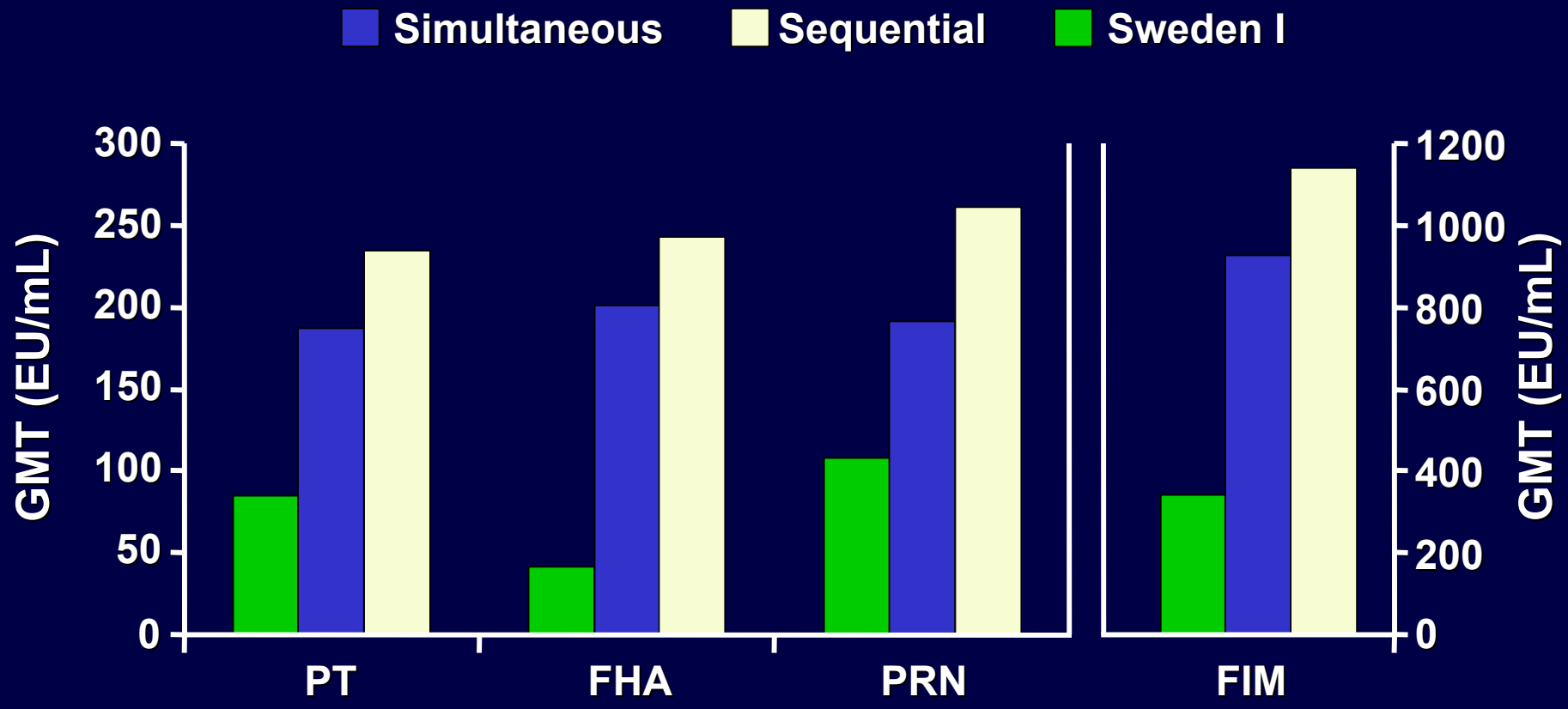
Simultaneous	316 of 353, 89.5%	353 of 354, 99.7%	278 of 353, 78.8%
Sequential	278 of 323, 86.1%	318 of 324, 98.1%	269 of 323, 83.3%

Td502: Adacel and Fluzone, HAI Titers % ≥ 1:40



Simultaneous	90 of 341, 26.4%	295 of 341, 86.5%	12 of 341, 3.5%	184 of 341, 54.0%	71 of 341, 20.8%	275 of 341, 80.6%
Sequential	61 of 294, 20.7%	261 of 294, 88.8%	10 of 294, 3.4%	138 of 294, 46.9%	58 of 297, 19.5%	273 of 295, 80.3%

Td502: Adacel and Fluzone, Pertussis GMTs

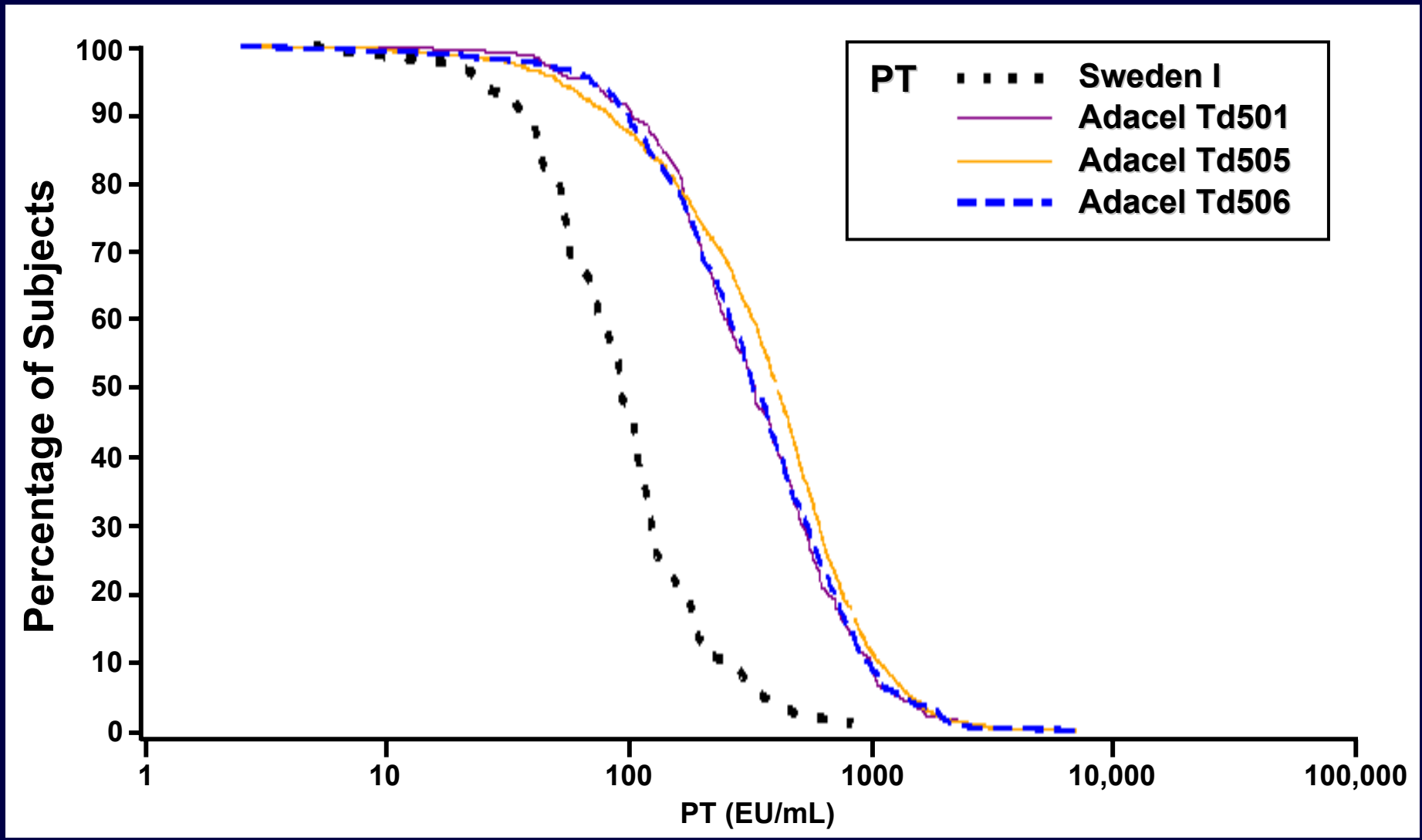


Simultaneous	186.4	200.6	191.7	925.8
Sequential	234.5	242.2	260.3	1136.3
Sweden I	86.6	40.0	108.1	341.1

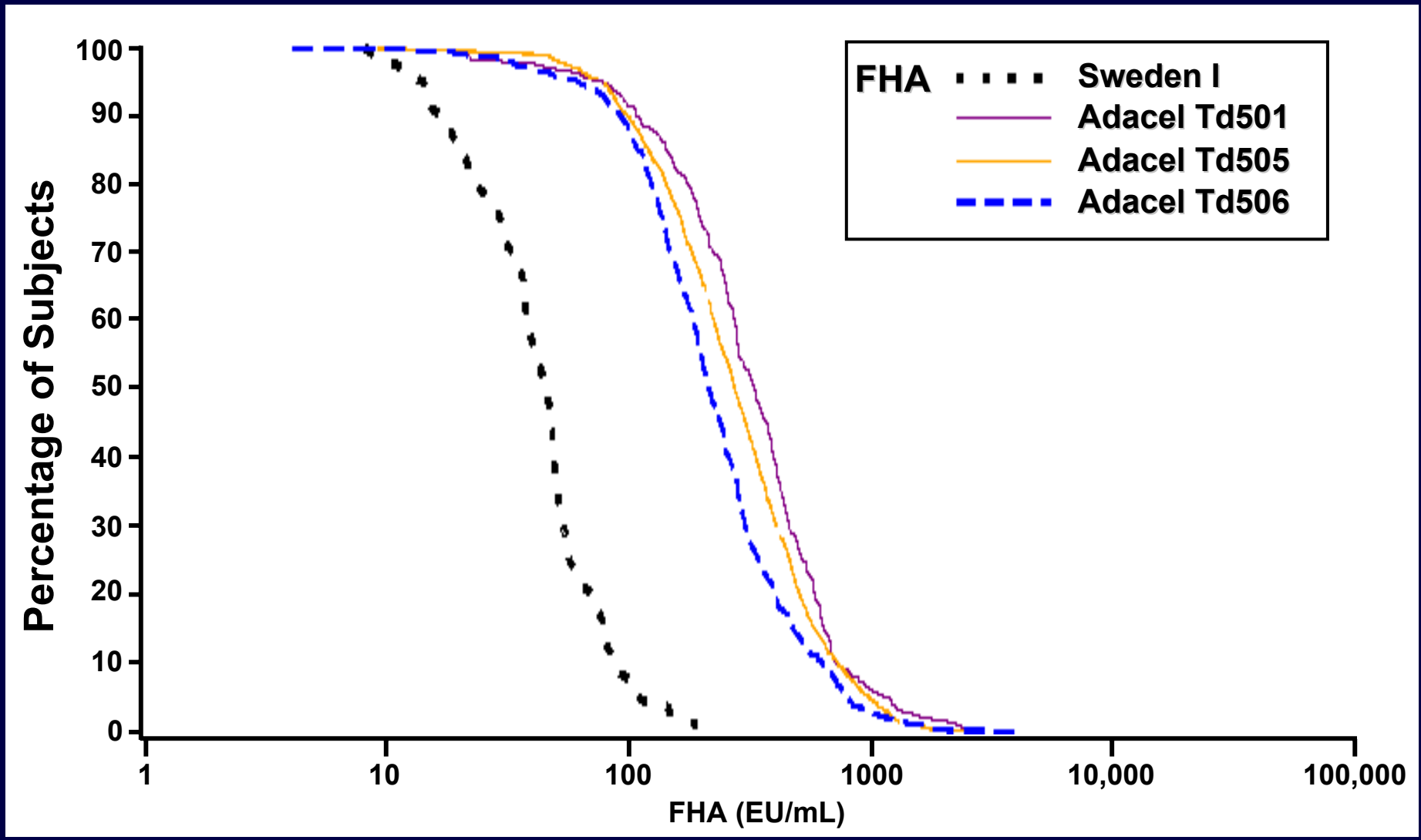
Td502: Simultaneous vs. Sequential Adacel and Influenza Vaccine Conclusions

- **Simultaneous and sequential vaccination resulted in comparable immune responses for:**
  - **Diphtheria and tetanus**
  - **Influenza (all 3 strains)**
- **Pertussis responses were somewhat reduced with concomitant influenza vaccine, but pertussis GMTs markedly exceeded those from Sweden I**
- **Adacel can be administered concomitantly with influenza vaccine**

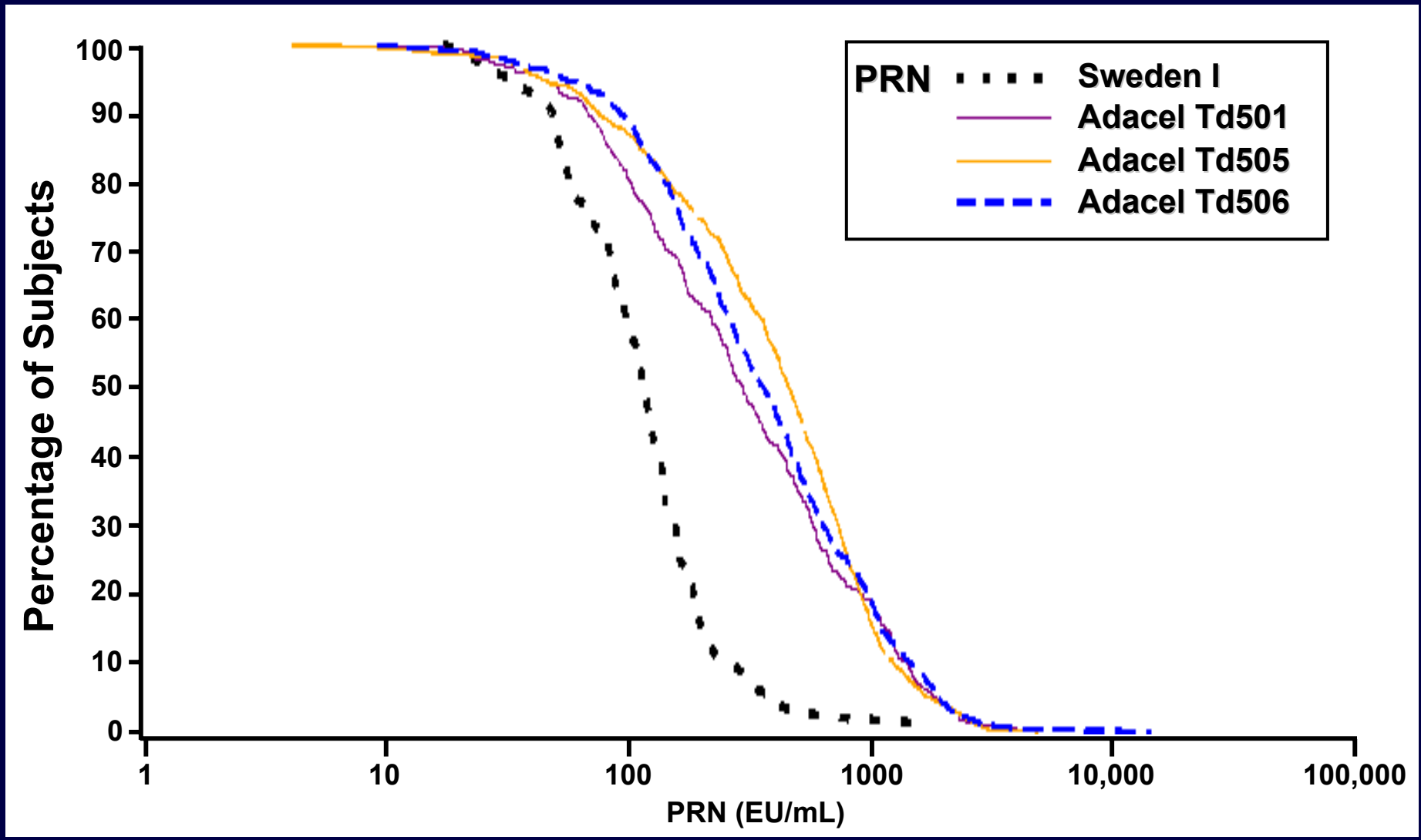
PT Antibody Responses in Adolescents: Sweden I vs. Td501, Td505, and Td506



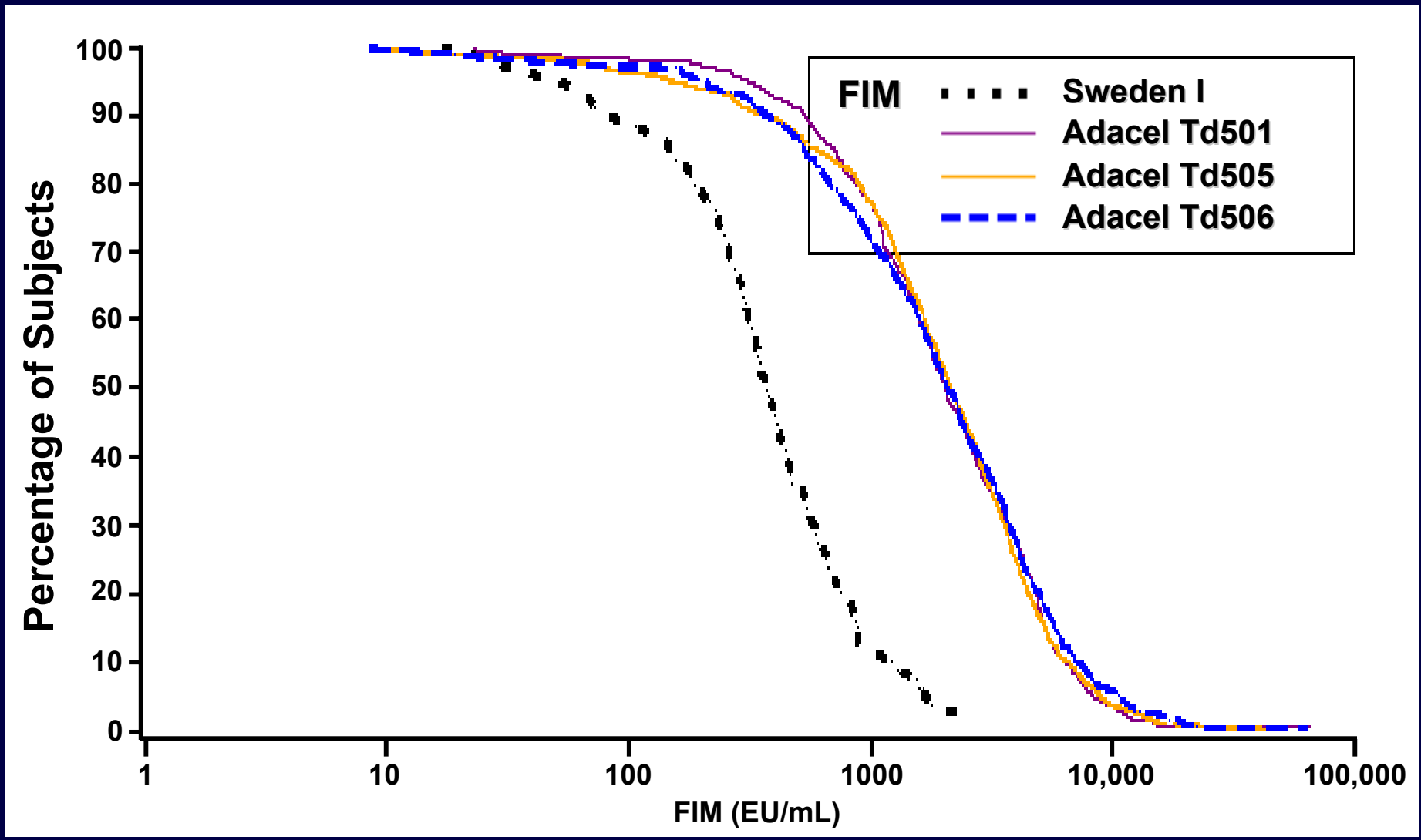
FHA Antibody Responses in Adolescents: Sweden I vs. Td501, Td505, and Td506



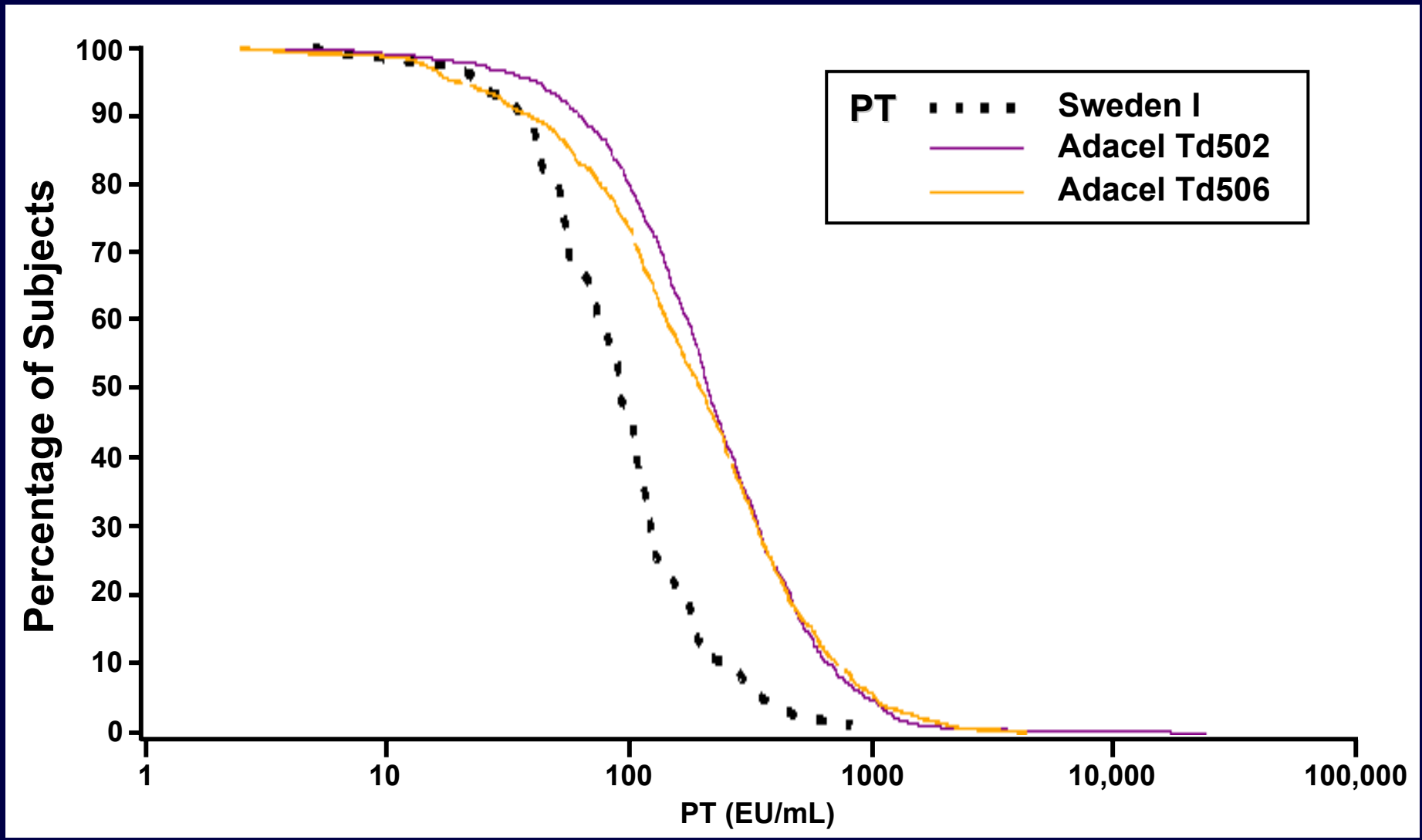
PRN Antibody Responses in Adolescents: Sweden I vs. Td501, Td505, and Td506



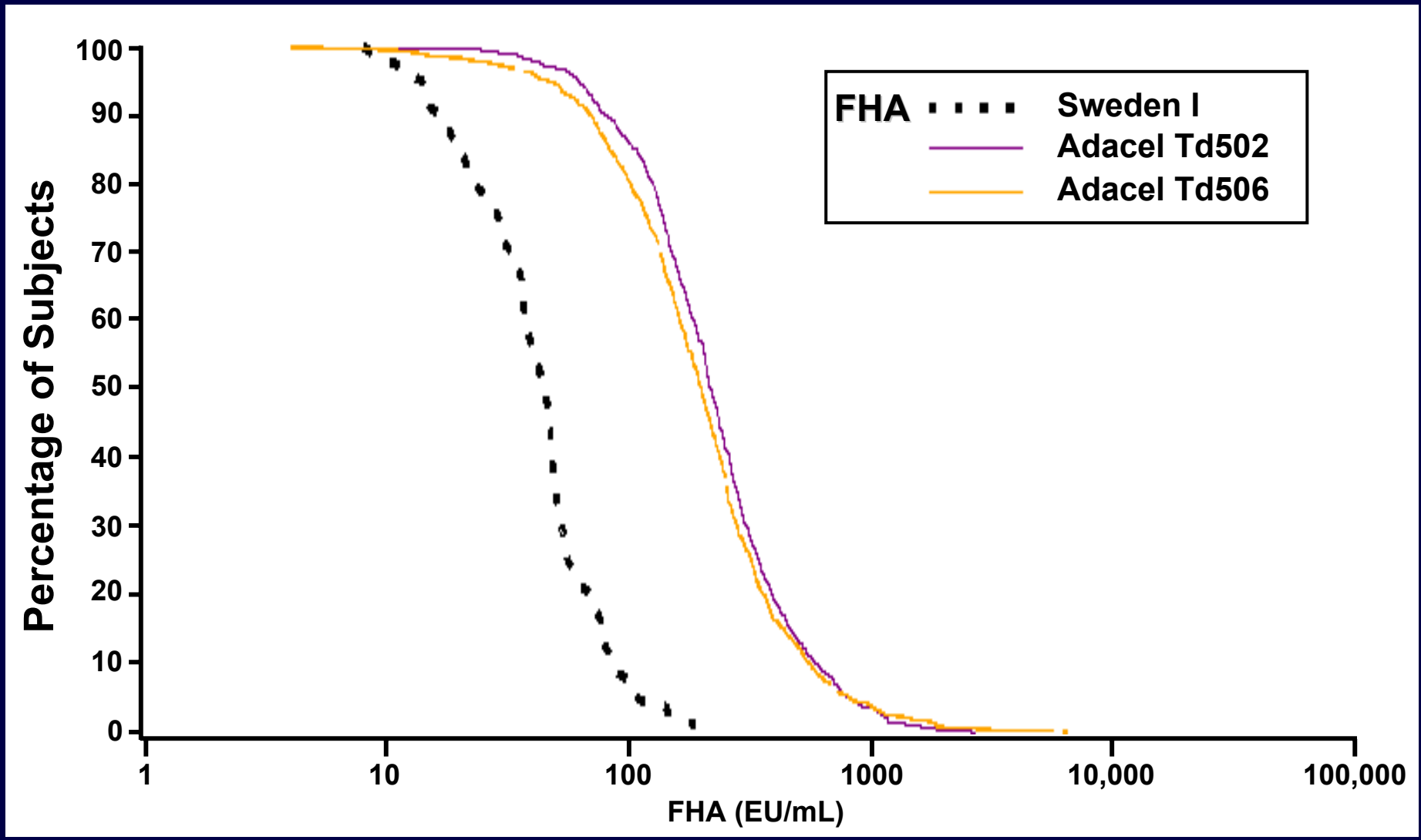
FIM Antibody Responses in Adolescents: Sweden I vs. Td501, Td505, and Td506



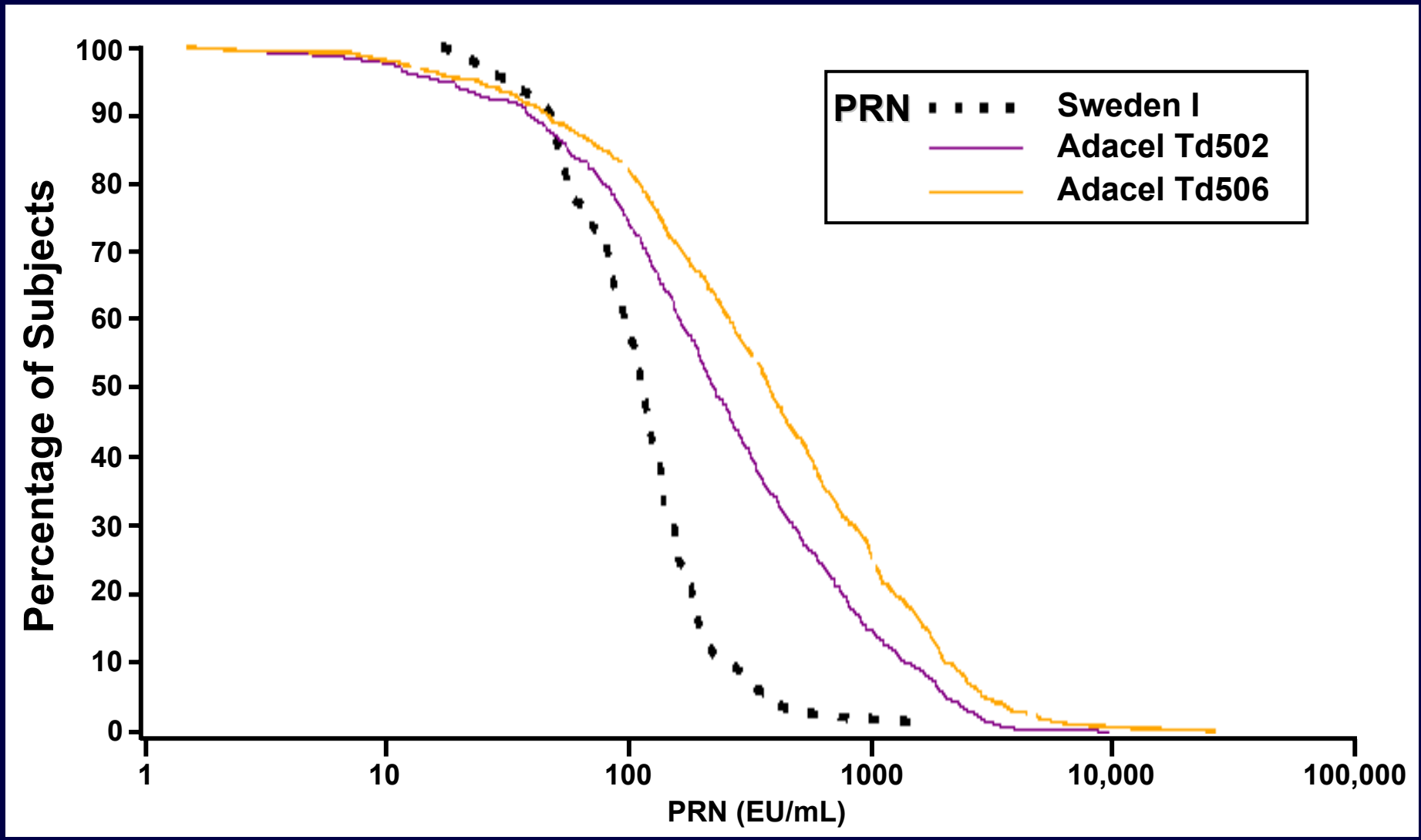
PT Antibody Responses in Adults: Sweden I vs. Td502 and Td506



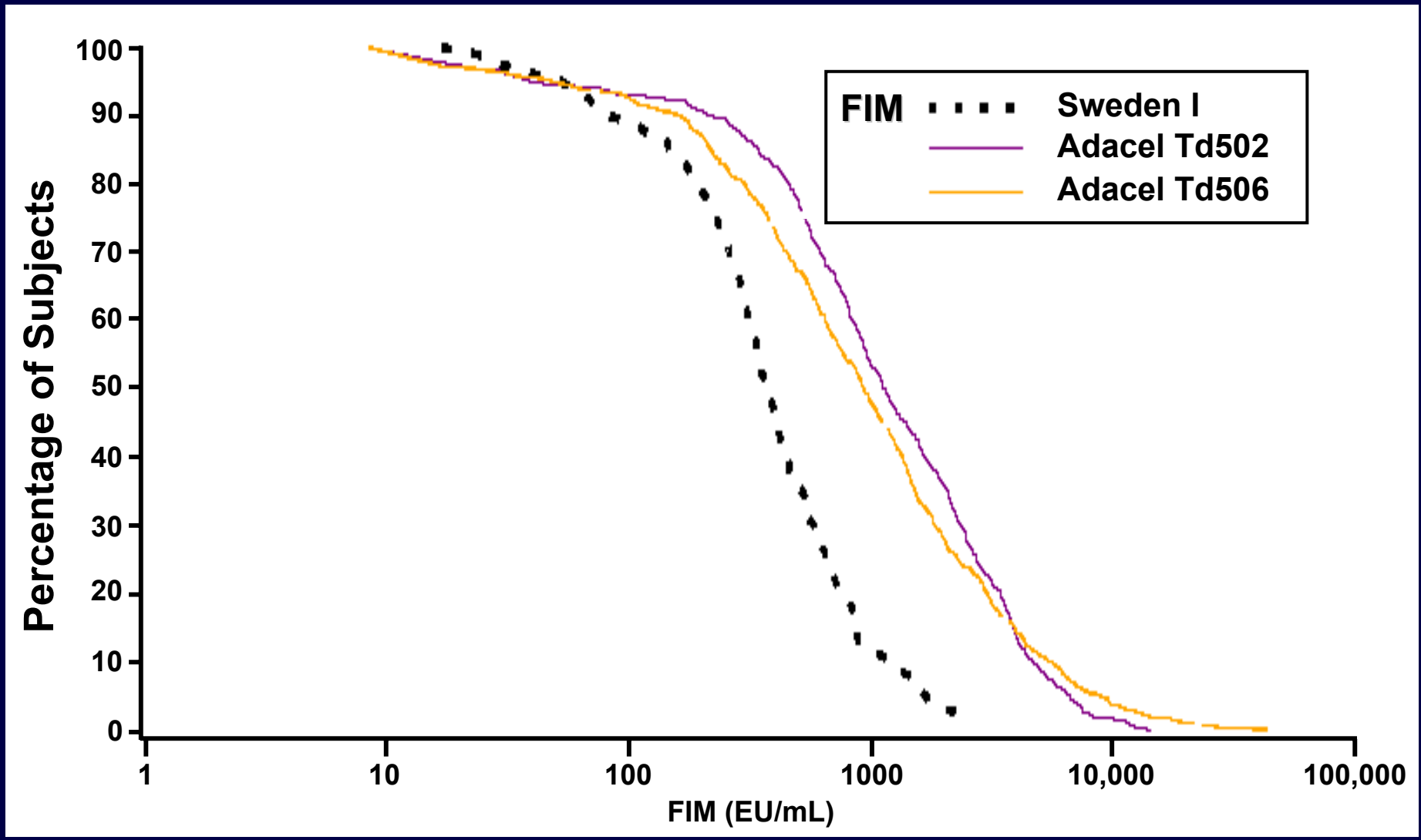
FHA Antibody Responses in Adults: Sweden I vs. Td502 and Td506



PRN Antibody Responses in Adults: Sweden I vs. Td502 and Td506



FIM Antibody Responses in Adults: Sweden I vs. Td502 and Td506



Canadian Licensure Trials of Adacel

- **TC9704: Evaluation in adolescents and adults of Adacel vs. Td; evaluation of lot consistency**
- **Td9707: Evaluation in adults of Adacel vs. Td**
- **Td9805: Evaluation in young adolescents of concomitant Adacel and hepatitis B**

- **Subset populations from the 3 preceeding studies were evaluated for immunogenicity at 1, 3, and 5 years following receipt of Adacel**
- **Safety data were submitted in support of US licensure**

Adacel: Key Immunogenicity Findings

- **Adacel stimulated robust antibody responses to all included antigens**
- **Adacel achieved all pre-specified non-inferiority criteria for immunogenicity vs. Td**
- **Pertussis antibody levels in adolescents and adults following one dose of Adacel exceeded levels seen in infants following three doses of Daptacel (which were associated with 85% efficacy against WHO-defined pertussis)**
- **Adacel can be given concomitantly with HB vaccine or influenza vaccine**

Adacel - Agenda

Introduction	**Luc Kuykens, MD, MPH** VP Regulatory Affairs
Pertussis Epidemiology	**David Johnson, MD, MPH** Director Scientific and Medical Affairs
Immunogenicity	**Michael Decker, MD, MPH** VP Scientific and Medical Affairs
Safety and Conclusion	**Luc Kuykens, MD, MPH** **VP Regulatory Affairs**

Safety Objectives

- **To compare safety profile of Adacel to safety profile of Td**
  - **Demonstrate that rates of selected solicited local and systemic reactions reported by Adacel and Td recipients are comparable**
- **To characterize overall safety profile of Adacel given separately or simultaneously with HB or influenza vaccine**

Presentation Outline and Safety Data Collection

- **Immediate Reactions**
  - **30 minutes post vaccination**
- **Solicited Local and Systemic Reactions**
- **Unsolicited Adverse Events**
- **Events of Special Interest**
- **Serious Adverse Events**

Immediate Reactions: Adolescents and Adults

	Adacel N = 5841		Td Vaccine N = 1365	
	n	%	n	%
Total participants with at least one reaction	32	0.55	6	0.44
Most frequently reported events:				
Dizziness	6	0.10	1	0.07
Hypoaesthesia	3	0.05	1	0.07
Paraesthesia	2	0.03	1	0.07
Vasovagal attack	2	0.03	2	0.15
Pain in limb	2	0.03	0	0.0
Injection site bruising	2	0.03	0	0.0
Injection site erythema	3	0.05	0	0.0
Syncope	3	0.05	2	0.15
Injection site pain	1	0.02	0	0.0
Dyspepsia, Nausea, Vomiting	3	0.05	0	0.0
Other	13	0.22	1	0.07

Presentation Outline and Safety Data Collection

- Immediate Reactions
- **Solicited Local and Systemic Reactions**
  - **Erythema, swelling, pain, underarm lymph node swelling, and limb circumference, collected on diary card day 0 - 14, severity documented**
- Unsolicited Adverse Events
- Events of Special Interest
- Serious Adverse Events

Td506: Solicited Local Reactions Safety Hypothesis

Adacel is non-inferior to Td in the proportion of adolescents and adults with:

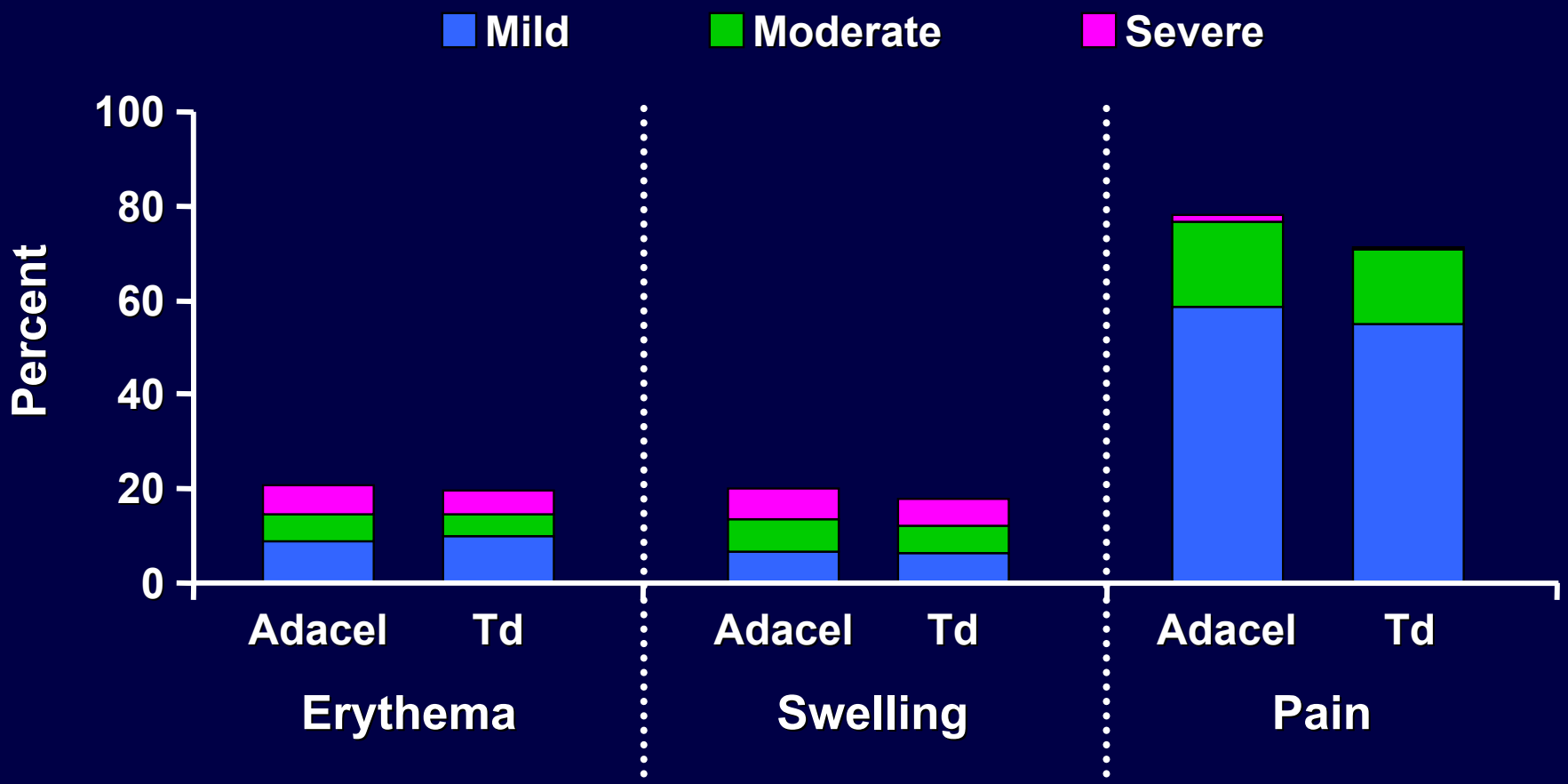
- **any erythema, swelling or pain, and with**
- **moderate and severe erythema, swelling or pain reported during Day 0 through Day 14.**

<u>Non-inferiority criteria:</u>

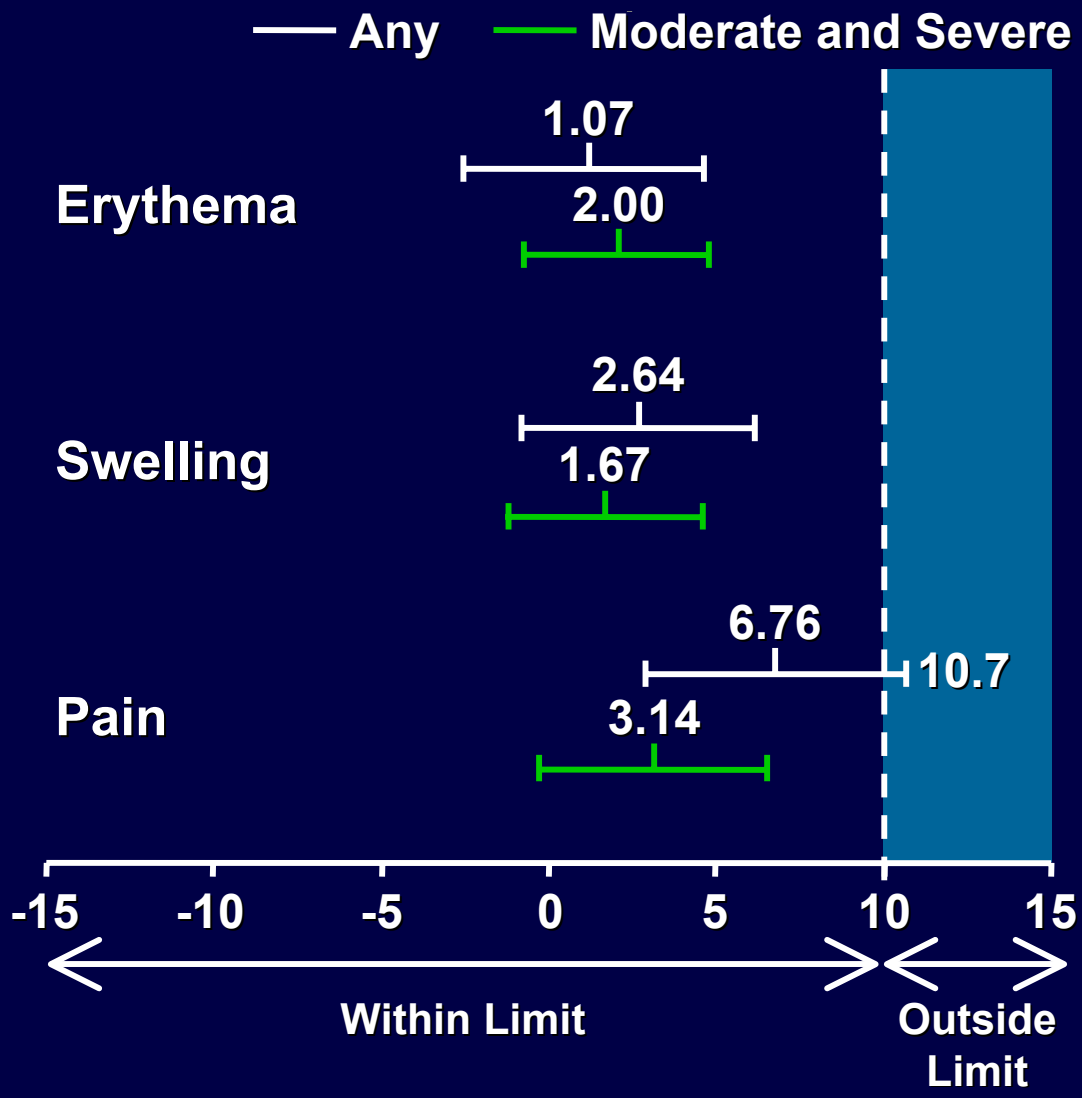
Upper limit of the two-sided

95% CI of the difference $p_{Adacel} - p_{Td} < 10\%$

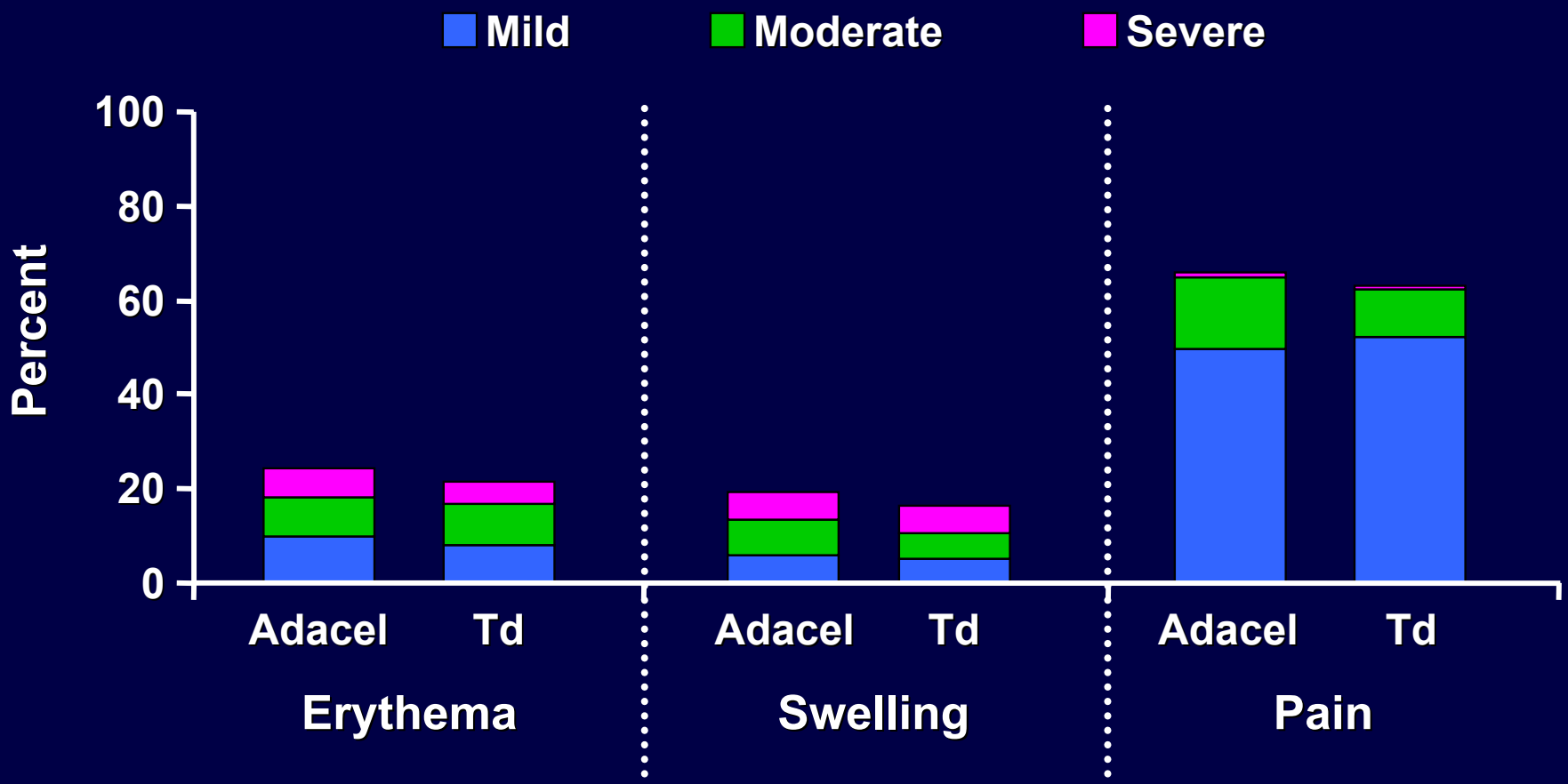
Td506: Solicited Local Reactions, Days 0-14 Adolescents



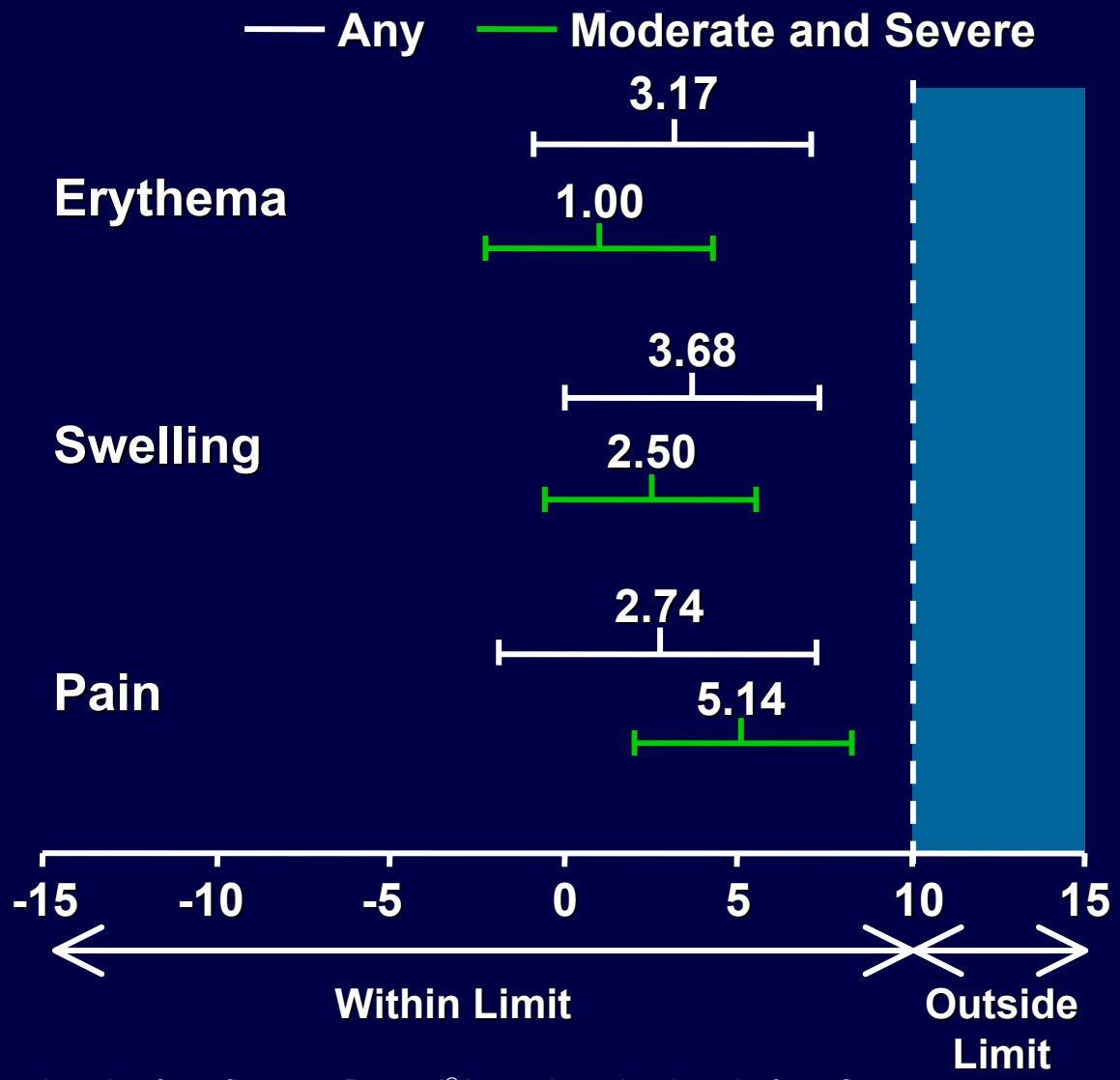
Td506: Non-Inferiority of Solicited Local Reactions, Days 0-14 Adolescents, 95% CI of Difference (Adacel minus Td)



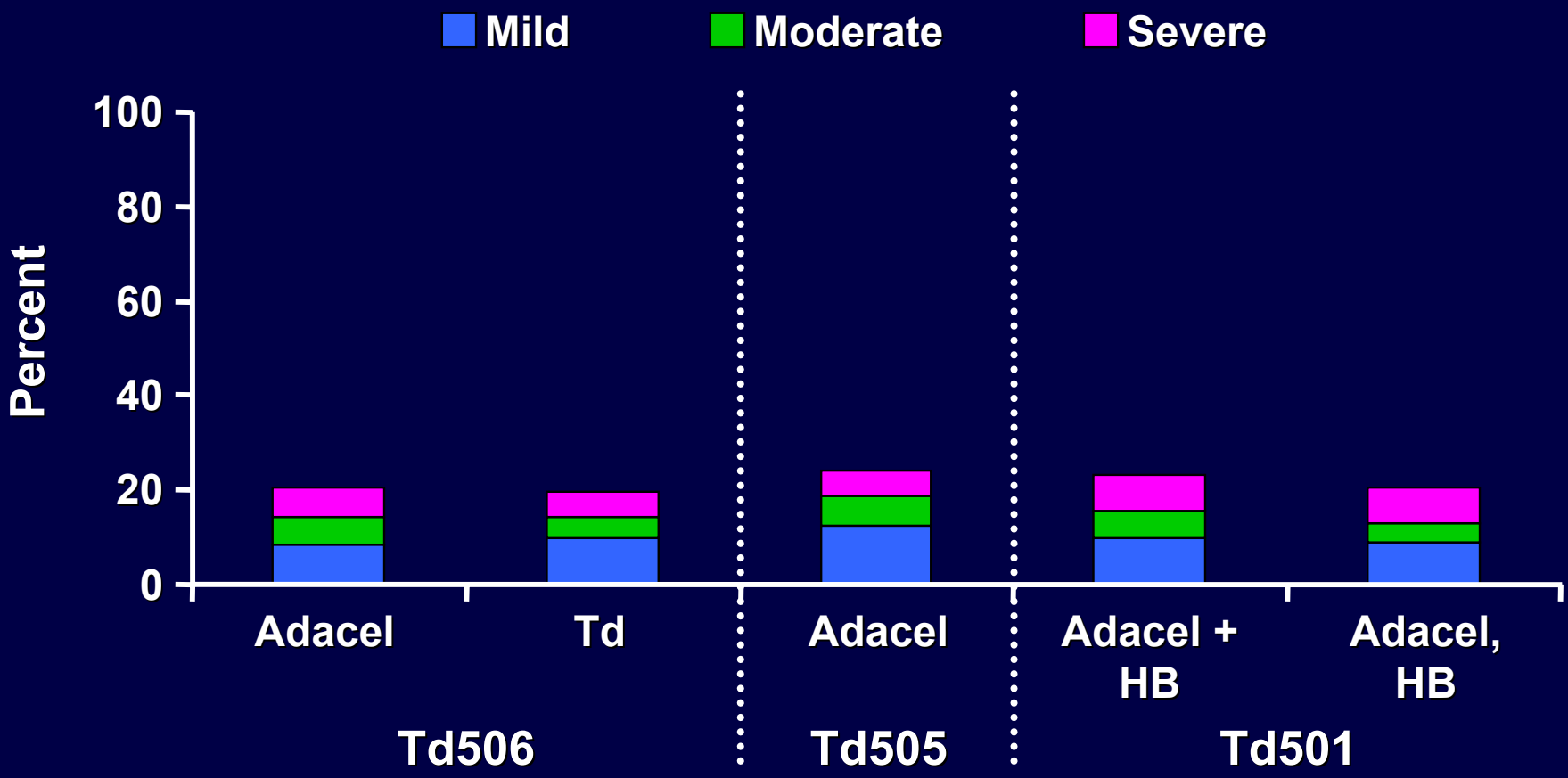
Td506: Solicited Local Reactions, Days 0-14 Adults



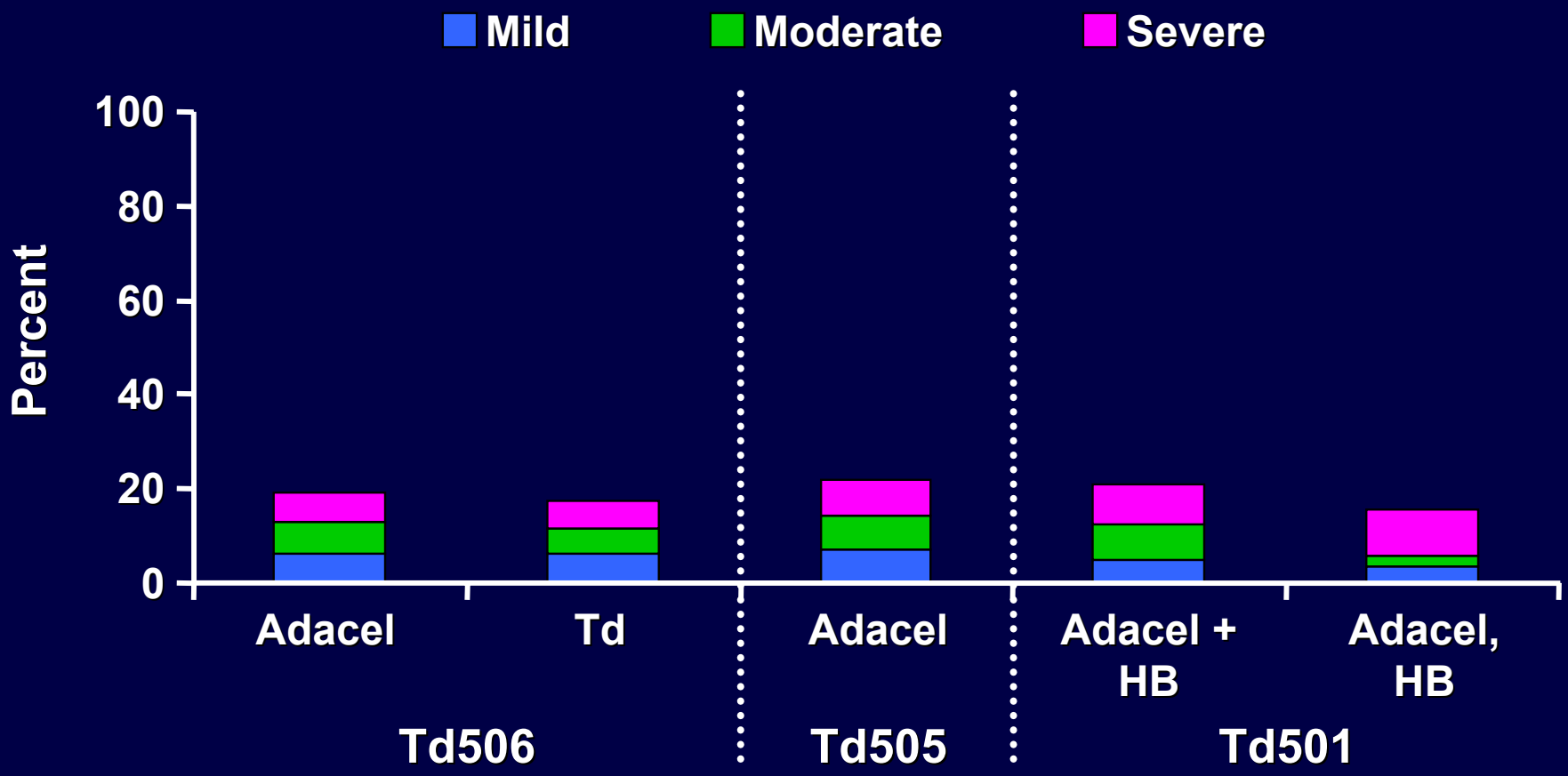
Td506: Non-Inferiority of Solicited Local Reactions, Days 0-14 Adults, 95% CI of Difference (Adacel minus Td)



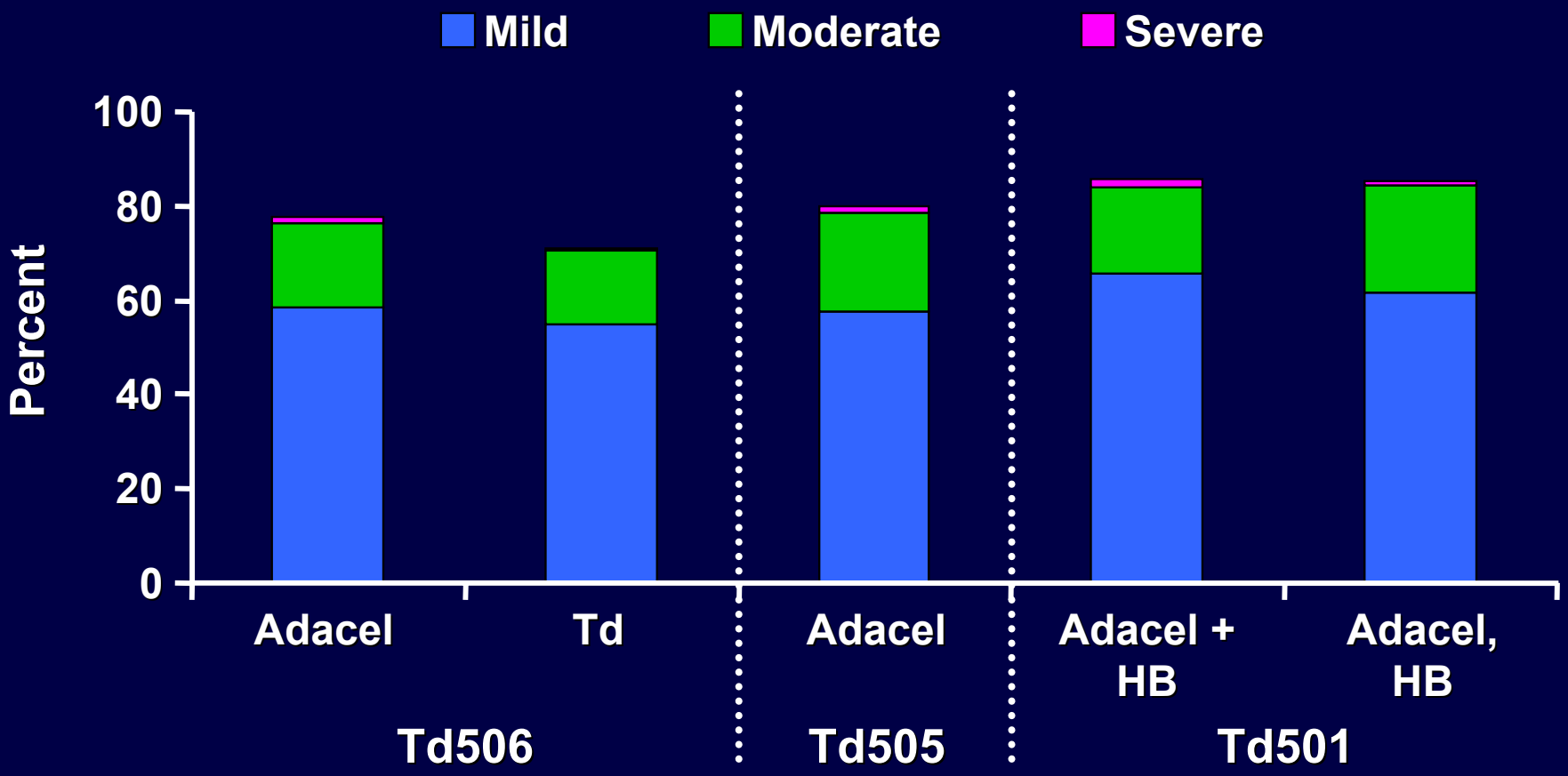
Erythema Rates, Days 0-14 Adolescents



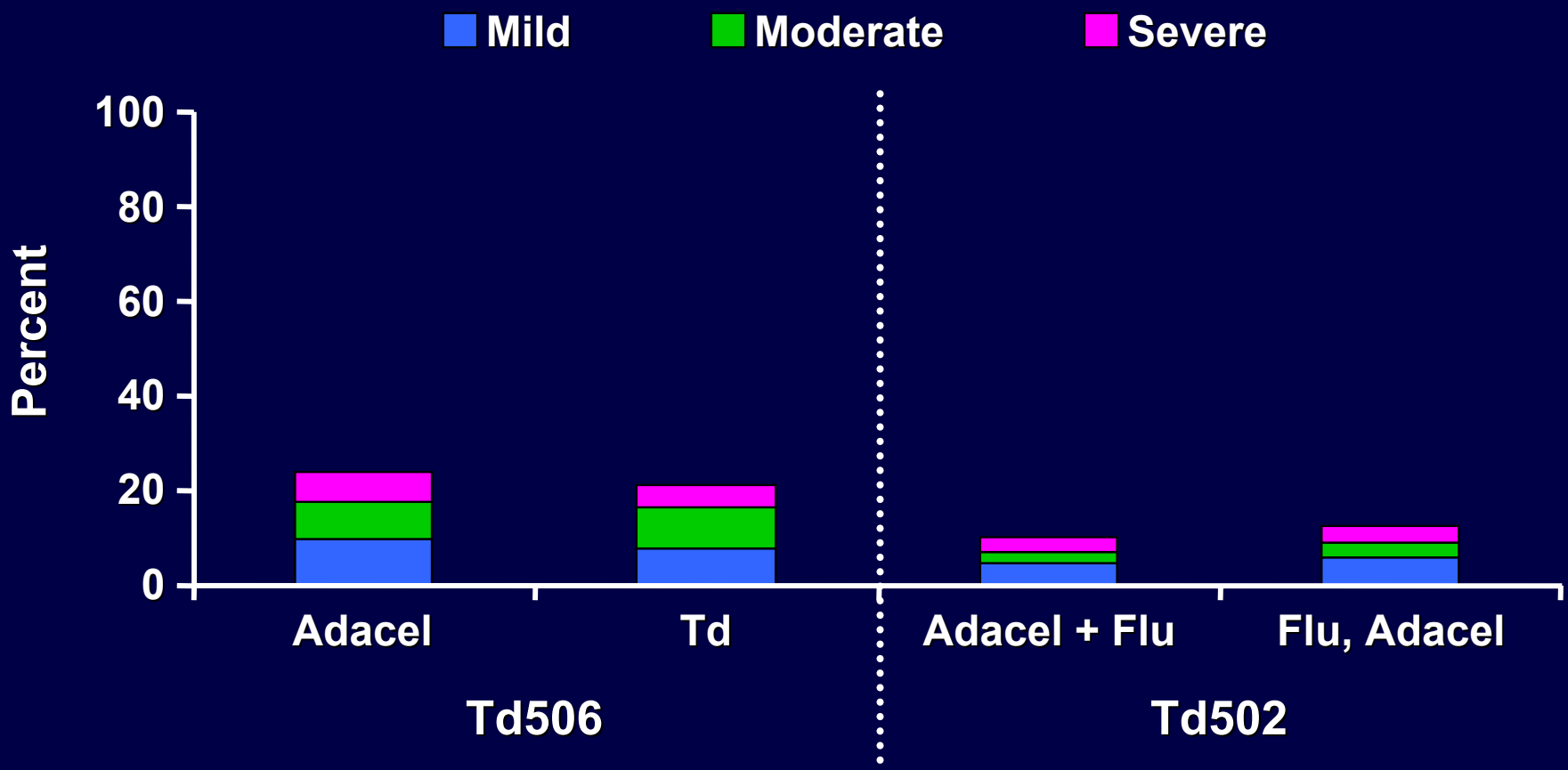
Swelling Rates, Days 0-14 Adolescents



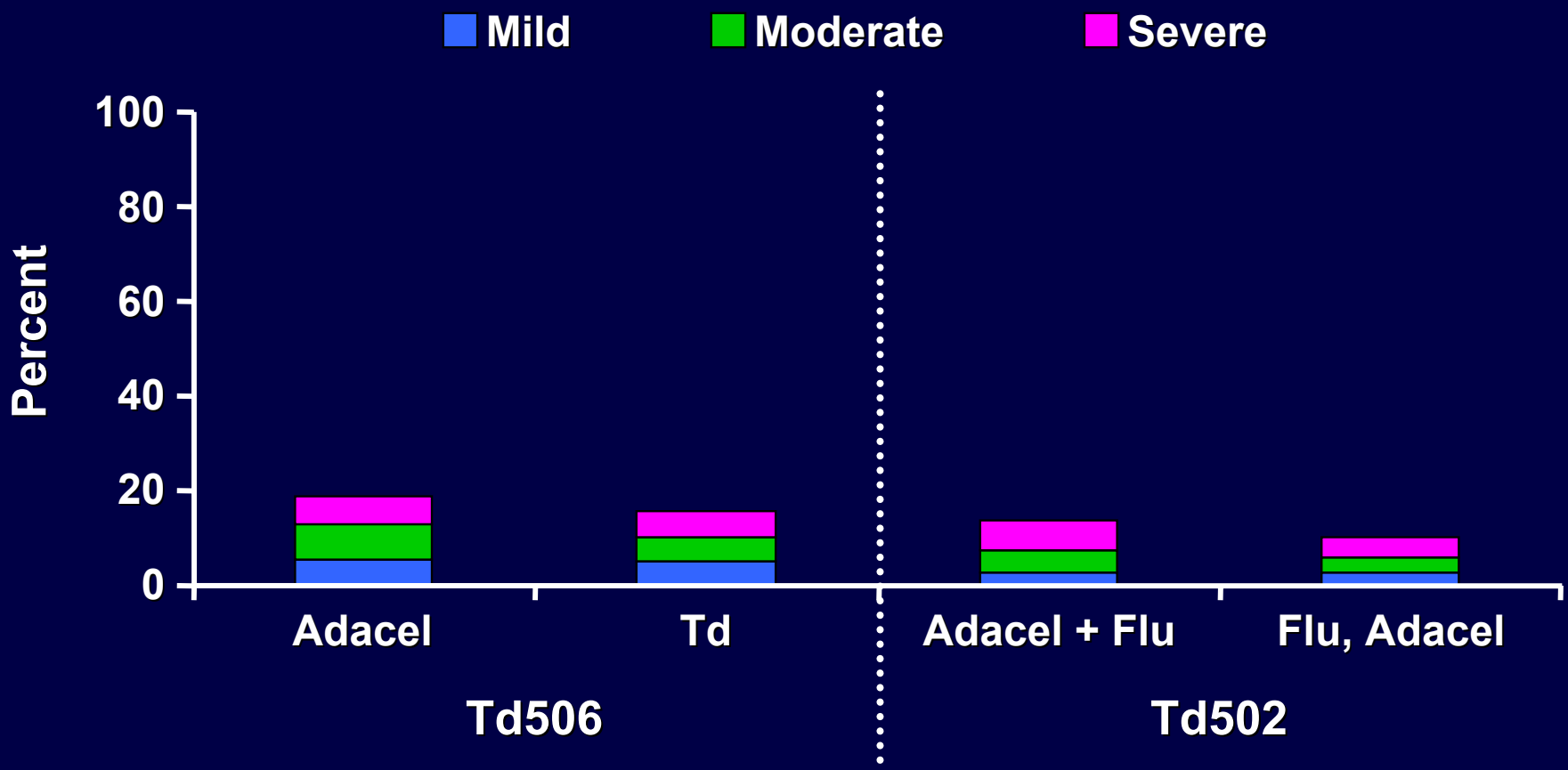
Pain Rates, Days 0-14
Adolescents



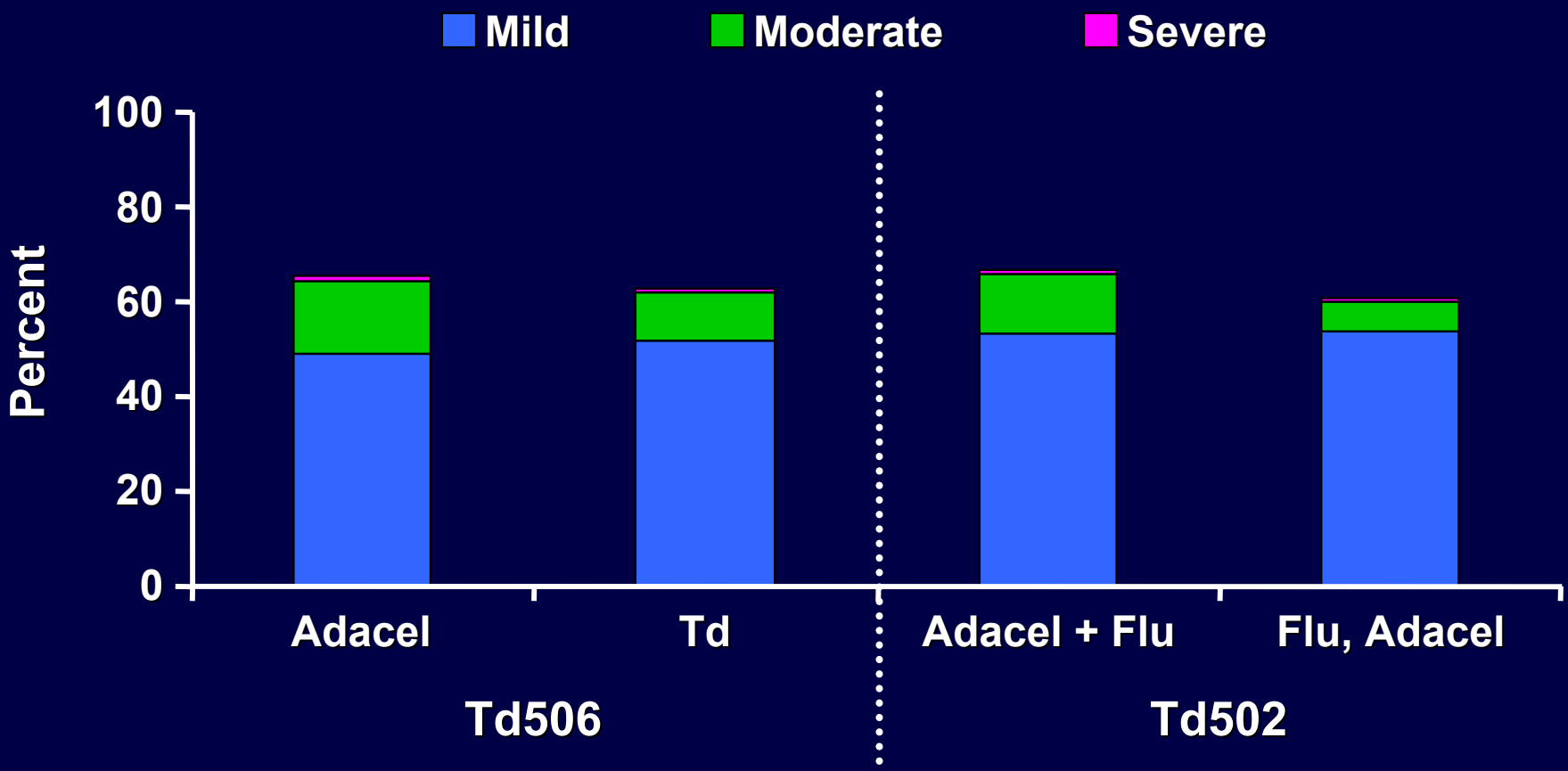
Erythema Rates, Days 0-14
Adults



Swelling Rates, Days 0-14
Adults



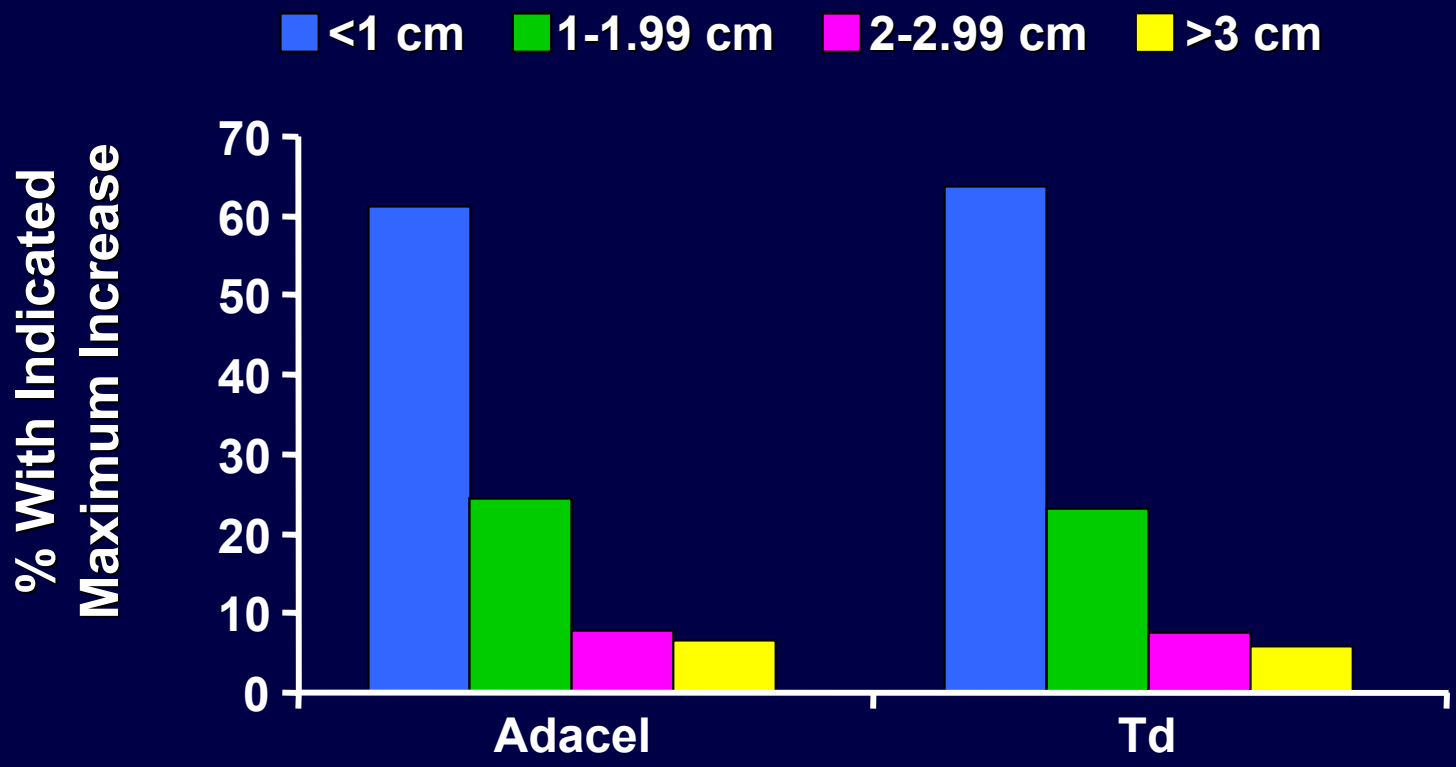
Pain Rates, Days 0-14
Adults



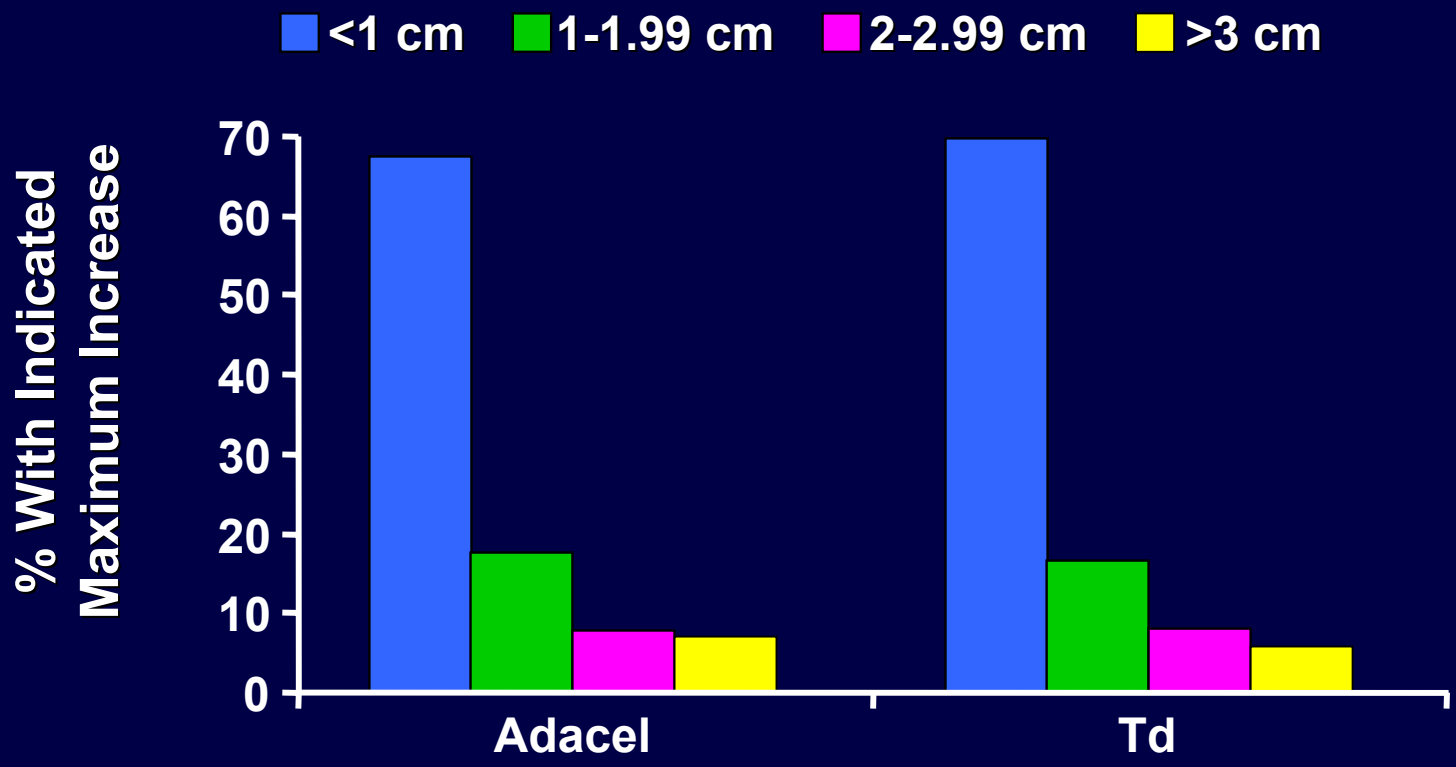
Other Solicited Local Reactions

- **Limb circumference**
  - **Mean baseline limb circumference in Td506**
    - **Adolescents: 26.4 cm**
    - **Adults: 31.7 cm**
  - **No difference in mean change observed in Td506 between Adacel and Td recipients**
    - **Adolescents 1.25 cm vs. 1.35 cm**
    - **Adults 1.51 cm vs. 1.29 cm**

Td506: Increase in Limb Circumference After Vaccination With Adacel vs. Td, Days 0-14, in Adolescents



Td506: Increase in Limb Circumference After Vaccination With Adacel vs. Td, Days 0-14, in Adults



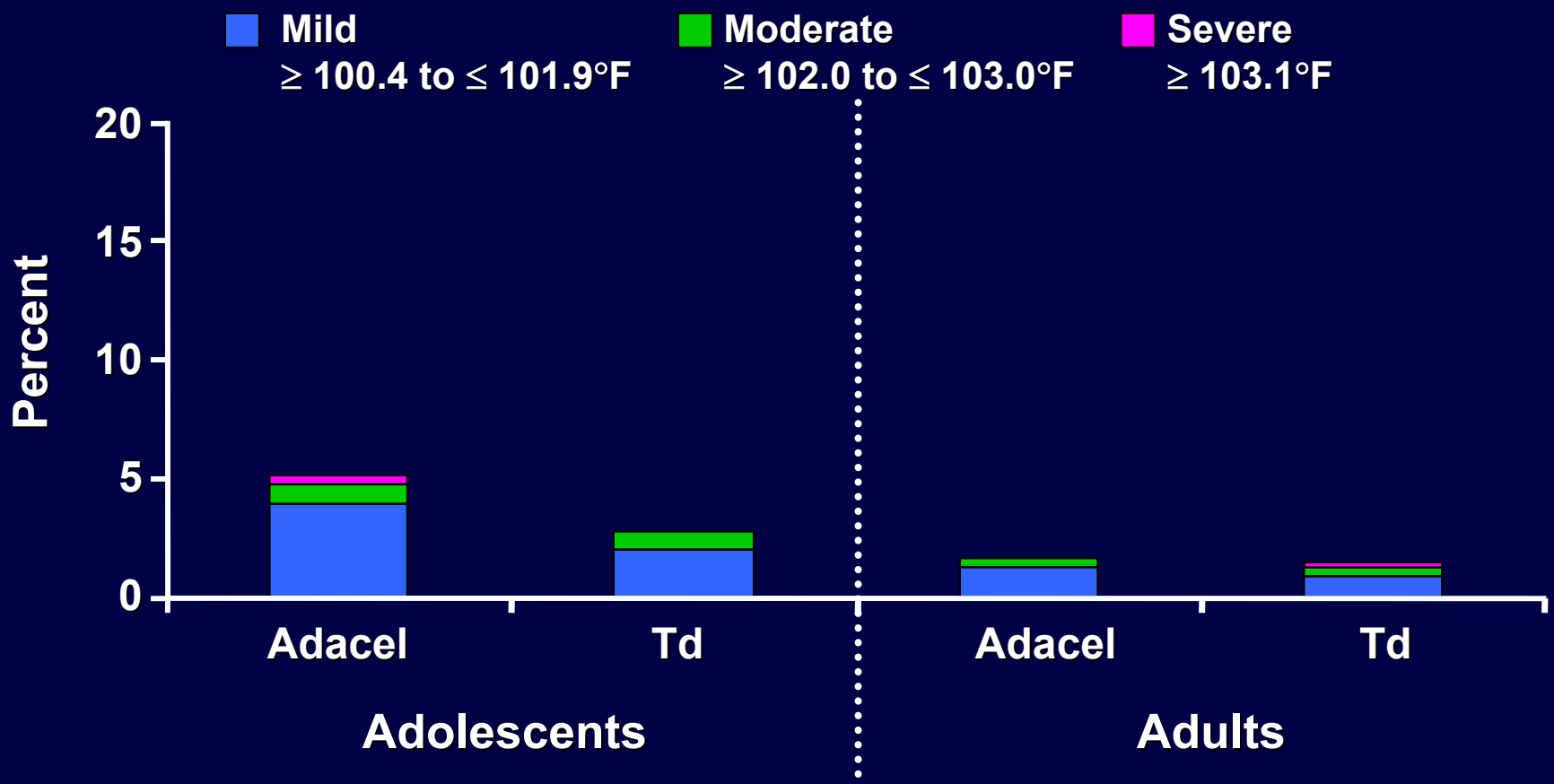
Other Solicited Local Reactions

- **Underarm Lymph Node swelling**
  - **No difference observed in Td506 between Adacel and Td recipients**
    - **Adolescents 6.64% vs. 5.34%**
    - **Adults 6.48% vs. 4.10%**
  - **Similar rates reported across three other studies**
    - **Adolescents 6.64% - 8.96%**
    - **Adults 3.83% - 6.48%**

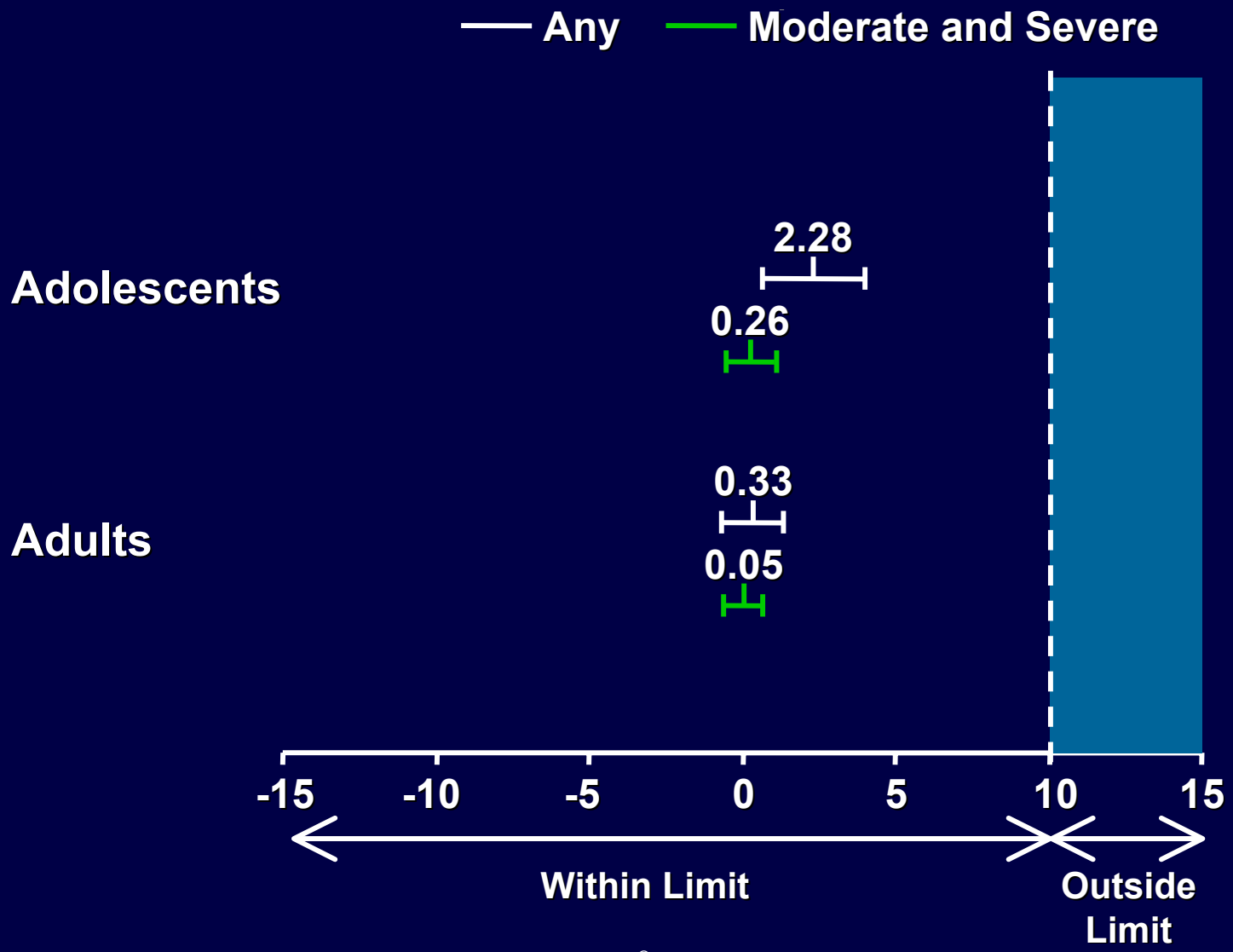
Presentation Outline and Safety Data Collection

- Immediate Reactions
- **Solicited Local and Systemic Reactions**
  - **Fever, headache, tiredness, generalized body ache, chills, nausea, vomiting, diarrhea, sore and/or swollen joints, and rash, collected on diary card day 0 - 14, severity documented**
- Unsolicited Adverse Events
- Events of Special Interest
- Serious Adverse Events

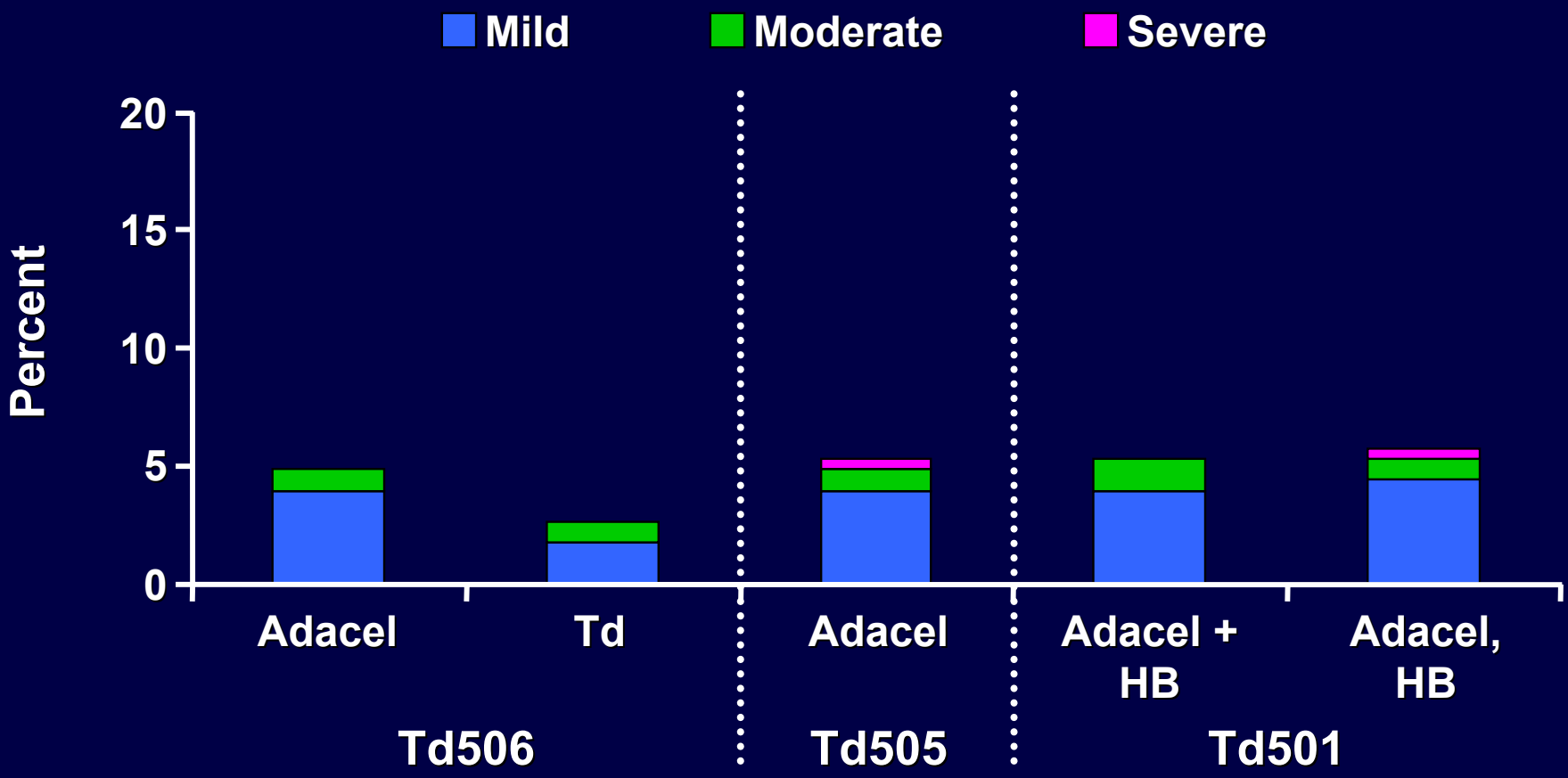
Td506: Fever, Days 0-14
Adolescents and Adults



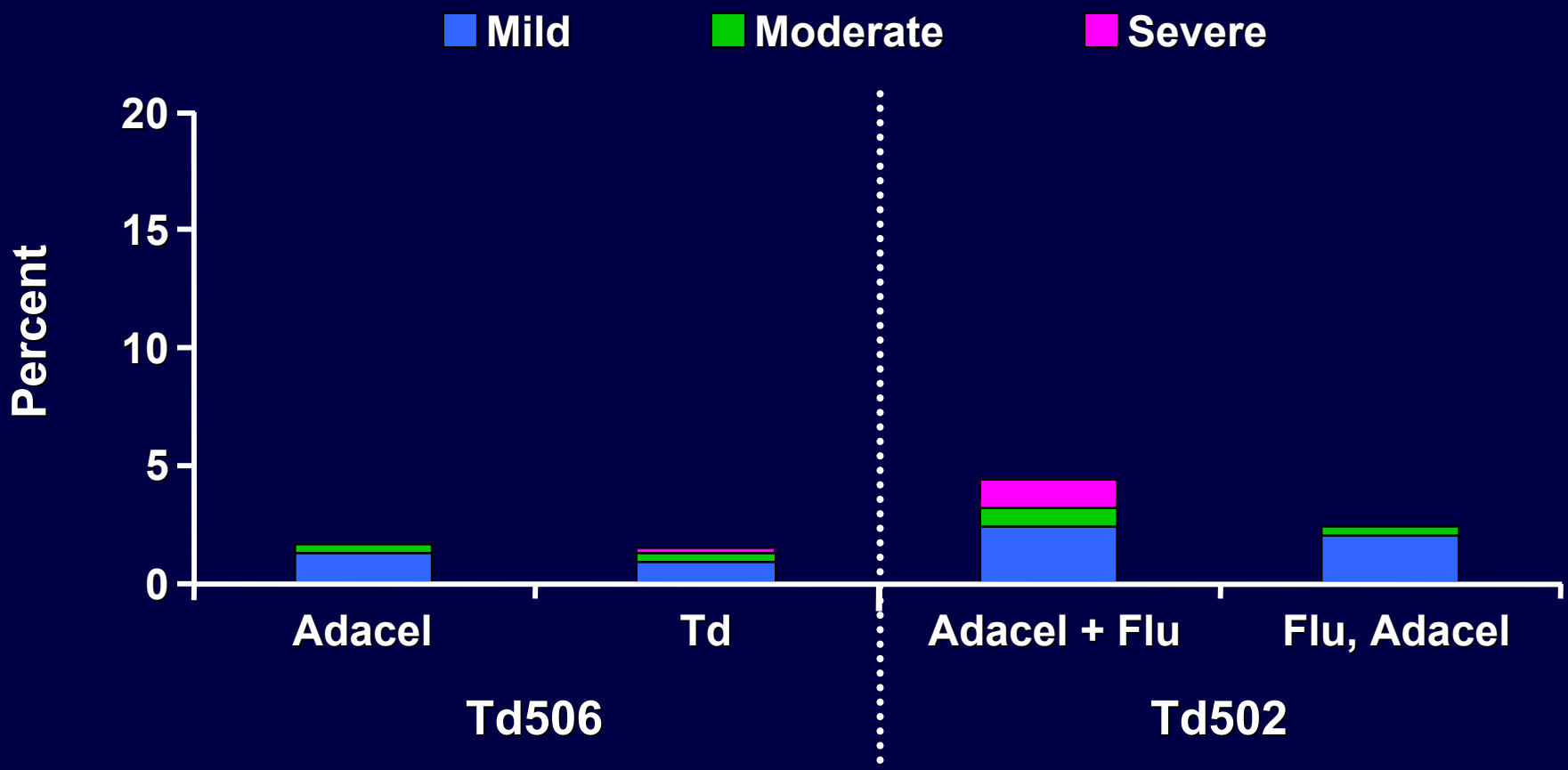
Td506: Fever, Non-Inferiority of Rates, Days 0-14
95% CI of Difference (Adacel minus Td)



Fever Rates, Days 0-14
Adolescents



Fever Rates, Days 0-14
Adults



Td506: 'Any' Systemic Reaction Profile Adolescents

	Adacel N = 1184 %	Td Vaccine N = 792 %
Total participants with any systemic reaction	65.5	61.0
Headache	43.7	40.4
Tiredness	30.2	27.3
Bodyache	30.4	29.9
Chills	15.1	12.6
Nausea	13.3	12.3
Diarrhea	10.3	10.2
Sore/Swollen Joints	11.3	11.7
Vomiting	4.6	2.8
Rash	2.7	2.0

Td506: 'Any' Systemic Reaction Profile Adults

	Adacel N = 1752 %	Td Vaccine N = 573 %
Total participants with any systemic reaction	50.3	47.6
Headache	33.9	34.1
Tiredness	24.3	20.7
Bodyache	21.9	18.8
Chills	8.1	6.6
Nausea	9.2	7.9
Diarrhea	10.3	11.3
Sore/Swollen Joints	9.1	7.0
Vomiting	3.0	1.8
Rash	2.0	2.3

Presentation Outline and Safety Data Collection

- Immediate Reactions
- Solicited Local and Systemic Reactions
- **Unsolicited Adverse Events and Unsolicited Adverse Events Requiring Medical Contact**
  - **Collected from days 0 to 14 and day 15 to end of study, respectively, following Adacel or Td vaccination**
- Events of Special Interest
- Serious Adverse Events

All Studies: Unsolicited Adverse Events Reported by ≥ 1% of Participants/Group During Days 0-28 Post-Vaccination, ITTS Population - Adolescents

Adverse Event	Adacel N = 3393 %	Td Vaccine N = 792 %
Total Participants with any unsolicited AEs	24.0	25.6
Nasopharyngitis	3.24	4.29
Pharyngitis	3.18	3.54
Cough	2.18	2.53
Nasal congestion	1.68	0.88
Upper respiratory tract infection nos	1.00	1.39
Dysmenorrhoea	0.85	1.14
Sinusitis nos	0.68	1.26
Limb injury nos	0.32	1.01

All Studies: Unsolicited Adverse Events Reported by ≥ 1% of Participants/Group During Days 0-28 Post-Vaccination, ITTS Population - Adults

Adverse Event	Adacel N = 2448 %	Td Vaccine N = 573 %
Total Participants with any unsolicited AEs	24.6	20.9
Nasopharyngitis	3.31	1.92
Pharyngitis	2.37	1.22
Cough	1.43	1.05
Back pain	1.14	0.87
Upper respiratory tract infection nos	1.10	0.87
Sinusitis nos	1.06	0.52
Dysmenorrhoea	0.94	1.05
Pain in limb	0.65	1.22
Arthralgia	0.49	1.05

Presentation Outline and Safety Data Collection

- Immediate Reactions
- Solicited Local and Systemic Reactions
- Unsolicited Adverse Events and Unsolicited Adverse Events Requiring Medical Contact
- **Events of Special Interest**
  - **Whole Arm Swelling, Diabetes, Seizures and Autoimmune Disorders**
  - **Collected for entire study period (Td506- 6 months, Td505- 1 month, Td501- 5 or 6 months, Td502- 1 or 2 months)**
- Serious Adverse Events

New Onset Diabetes Mellitus, Seizures and Autoimmune Disorders

- **Two reports of new onset DM**
  - **One adolescent with a family history of IDDM**
  - **One adult with NIDDM discovered during an hospitalization for a trauma**
- **Three reports of seizures**
  - **Two adolescents, one each after Adacel and Td vaccination, both with a history of seizure disorder**
  - **One adult with a history of migraines and hypertension**
- **All events resolved without sequelae and were considered as not related to vaccination by the investigator**
- **There were no reports of autoimmune disorders from the US licensure trials**

Whole Arm Swelling

- **There were no reports of whole arm swelling from the US licensure trials**
- **There was no other evidence that whole arm swelling occurred**
  - **15 (0.26%) of 5841 Adacel recipients and 2 (0.15%) of 1365 Td recipients had injection site swelling ≥ 100mm days 0-14**
  - **Of the 5 subjects with injection site swelling ≥ 150mm days 0-14, none had an increase in limb circumference ≥ 2cm**

Presentation Outline and Safety Data Collection

- Immediate Reactions
- Solicited Local and Systemic Reactions
- Unsolicited Adverse Events and Unsolicited Adverse Events Requiring Medical Contact
- Events of Special Interest
- **Serious Adverse Events**
  - **Collected for entire study period (Td506- 6 months, Td505- 1 month, Td501- 5 or 6 months, Td502- 1 or 2 months)**

SAEs: All Trials, Day 0 up to 6 Months, Adolescents and Adults

- **Total participants reporting SAEs**
  - **Adacel - 52 of 5841 (0.89%)**
  - **Td vaccine - 19 of 1365 (1.39%)**
- **All except two reported as unrelated to study vaccine**
  - **23 y/o female hospitalized for severe migraine and temporary unilateral palsy one day after vaccination, lasting 3 days, recovered without sequelae**
  - **49 y/o female developed radicular pain in the left upper arm 12 days post vaccination, recovered without sequelae**

Deaths

- **One death was reported across the 4 studies, in Td505**
  - **15 year old female committed suicide, 70 days after receiving Adacel**
  - **Classified by investigator as unrelated to study vaccine**

Adacel - Agenda

Introduction	Luc Kuykens, MD, MPH VP Regulatory Affairs
Pertussis Epidemiology	David Johnson, MD, MPH Director Scientific and Medical Affairs
Immunogenicity	Michael Decker, MD, MPH VP Scientific and Medical Affairs
Safety and Conclusion	**Luc Kuykens, MD, MPH** **VP Regulatory Affairs**

Safety

- Adacel was safe and well tolerated among adolescents and adults
- Adacel achieved all safety non-inferiority endpoints in the primary comparative trial vs. Td, except for any pain in adolescents
- Adacel can be safely administered either concomitantly or sequentially with hepatitis B vaccine or influenza vaccine

Immunogenicity

- **Adacel achieved all pre-specified non-inferiority criteria for immunogenicity vs. Td**
- **Pertussis antibody levels in adolescents and adults following one dose of Adacel exceeded levels seen in infants following three doses of Daptacel (which were associated with 85% efficacy against WHO-defined pertussis)**
- **Adacel can be given concomitantly with hepatitis B vaccine or influenza vaccine**

Risk / Benefit

Risks

- Slight increase in reactogenicity in adolescents compared to Td

Benefits

- Adacel provides tetanus and diphtheria immunogenicity similar to current standard of care, Td
- Added protection against pertussis in adolescents and adults
- Potential to reduce pertussis disease in general population and prevent transmission of pertussis from adolescents and adults to infants

Vaccine and Related Biological Products Advisory Committee

March 15, 2005

ADACEL™

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed

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